June 4, 2003

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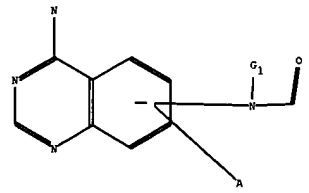

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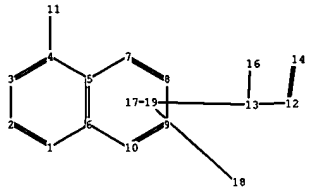

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11 12 13 14 16 18 20
ring nodes :
1 2 3 4 5 6 7 8 9 10
chain bonds :
4-11 12-13 12-14 13-16
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10
exact/norm bonds :
4-11 12-13 12-14 13-16
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 8-9 9-10

G1:H,CH3,Et,n-Pr,i-Pr

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
10:Atom 11:CLASS 12:CLASS 13:CLASS 14:CLASS 16:CLASS 17:CLASS
18:CLASS 19:CLASS 20:Atom

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=> d his

     (FILE 'HOME' ENTERED AT 15:24:13 ON 04 JUN 2003)

     FILE 'REGISTRY' ENTERED AT 15:24:36 ON 04 JUN 2003
L1               STRUCTURE UPLOADED
L2               QUE L1
L3            20 S L2
L4           476 S L2 SSS FUL

     FILE 'CAPLUS' ENTERED AT 15:25:16 ON 04 JUN 2003
L5            70 S L4

     FILE 'REGISTRY' ENTERED AT 15:25:39 ON 04 JUN 2003
L6               STRUCTURE UPLOADED
L7               QUE L6
L8            21 S L7  SUB=L4 SAM
L9           337 S L7  SUB=L4 FUL
L10          139 S L4 NOT L9

     FILE 'CAPLUS' ENTERED AT 15:27:11 ON 04 JUN 2003
L11           45 S L9
L12          ANALYZE L11 1- RN HIT :     335 TERMS

     FILE 'REGISTRY' ENTERED AT 15:27:30 ON 04 JUN 2003
L13            1 S 289499-45-2/RN
L14          336 S L9 NOT L13

     FILE 'CAPLUS' ENTERED AT 15:29:52 ON 04 JUN 2003
L15           27 S L14
L16            2 S L13 AND L15
L17           27 S L15 OR L16

=> d l2
L2 HAS NO ANSWERS
L1               STR
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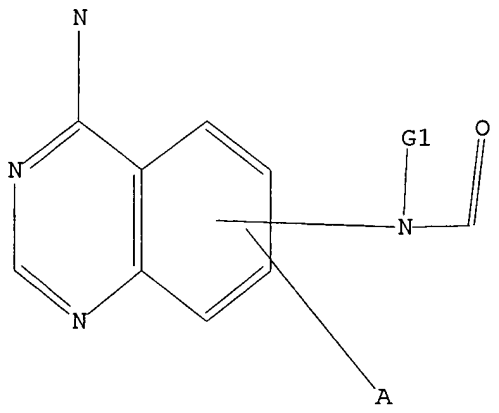


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G1 H,Me,Et,n-Pr,i-Pr


Structure attributes must be viewed using STN Express query preparation.
L2               QUE  ABB=ON  PLU=ON  L1
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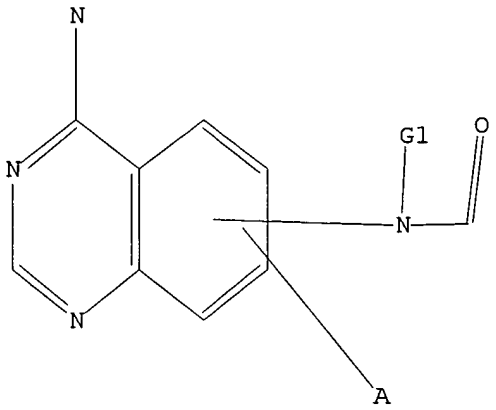
L7 HAS NO ANSWERS
L6 STR



Hy

G1 H,Me,Et,n-Pr,i-Pr

Structure attributes must be viewed using STN Express query preparation.
L7 QUE ABB=ON PLU=ON L6

=> d bib abs hitstr l17 1-27

L7 ANSWER 1 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:658094 CAPLUS
DN 137:185509
TI Preparation of 4-phenylaminoquinazoline derivatives as inhibitors of tyrosine-specific protein kinase
IN Kitano, Yasunori; Kawahara, Eiji; Suzuki, Tsuyoshi; Abe, Daisuke; Nakajou, Masahiro; Ueda, Naoko
PA Mitsubishi Pharma Corporation, Japan
SO PCT Int. Appl., 154 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002066445	A1	20020829	WO 2002-JP1575	20020221

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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PRAI JP 2001-45827 A 20010221
JP 2001-353525 A 20011119
OS MARPAT 137:185509
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. represented by the following general formula (I) or pharmaceutically acceptable salts thereof, hydrates or solvates of the same or mixts. of optically active isomers, racemic compds. or diastereomers of the same [n = an integer of 0-3; R1 = H, halo, HO, cyano, NO2, CF3, C1-5 alkyl, C1-5 alkoxy, S(O)f-C1-5 alkyl (wherein f = an integer of 0-2), (un)substituted NH2; one of R2 and R2 is R27SO2NH, (R28SO2)2N, C1-5 alkoxy, MeCOCH2CONH, MeSCH2CH2OCONH, or NCCH2CONH, etc. (wherein R27, R28 = optionally morpholino-substituted C1-5 alkyl) and the other one represents Y(CR12R13)mCR8R9C.tplbond.C, Y(CR12R13)mCR8R9CH:CH, Q, Q1 (wherein R8, R9 = H, optionally HO- or C1-5 alkoxy substituted C1-5 alkyl, or CR8 R9 together represent CO or C3-8 cycloalkylene optionally interrupted by O, S, NH, or alkyl-N; Y = H,HO, C1-5 alkoxy, C1-5 alkanoyloxy, etc.; R11, R12 = H, C1-5 alkyl; m = an integer of 0-3; p, q = 2,3; Z = O, S, SO, SO2, CO, optionally substituted NH; p1, p2 = an integer of 1-3; n1 = 0,1; W = H,HO, C1-5 alkoxy, C1-5 alkanoyloxy, CO2H, cyano, di-C1-5 alkyamino, morpholino, etc.)] are prepd. These compds. have an excellent protein kinase inhibitory activity specific to tyrosine and, therefore, are usable as drugs, in particular, remedies/preventives for various cancers, diseases caused by arteriosclerosis or psoriasis. Thus, 1-(1,1-dimethyl-2-propynyl)-4-methylpiperazine was treated with 4,4,5,5-tetramethyl-1,3,2-dioxaborane in the presence of PhCl(PPh3)3 in THF/CH2Cl2 at room temp. and coupled with 4-(3-chloro-4-fluorophenylamino)-6-methoxy-7-quinazolinyl triflate (prepn. given) in the presence of

PdCl2(dppf).CH2Cl2 [dppf = 1,1'-bis(diphenylphosphino)ferrocene] in a mixt. of DMF and 2 m aq. Na2CO3 80.degree. for 1 h to give the title compd. (II). II.HCl showed IC50 of 0.82 nM against EGF receptor tyrosine kinase.

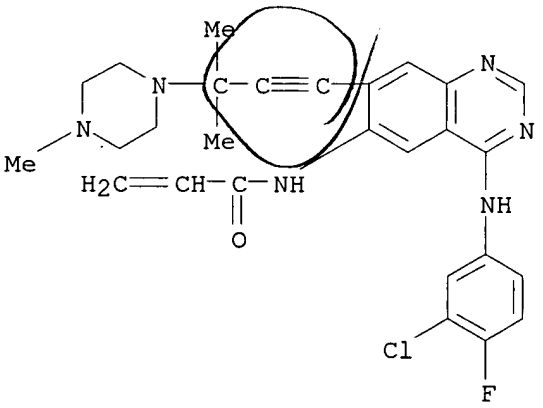
IT **451494-32-9P 451494-37-4P**

RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of phenylaminoquinazoline derivs. as inhibitors of tyrosine-specific protein kinase for prepn. and/or treatment of cancers, diseases caused by arteriosclerosis, or psoriasis)

RN 451494-32-9 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, hydrate (2:1) (9CI) (CA INDEX NAME)



●1/2 H_2O

RN 451494-37-4 CAPLUS

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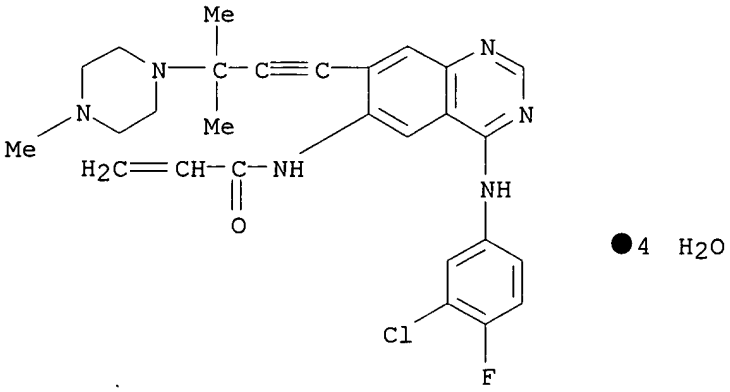
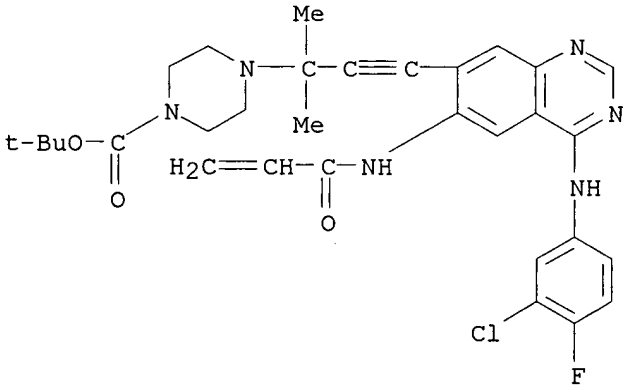


● 4 H_2O

● 3 HCl

IT **451493-21-3P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of phenylaminoquinazoline derivs. as inhibitors of tyrosine-specific protein kinase for prepn. and/or treatment of cancers, diseases caused by arteriosclerosis, or psoriasis)
RN 451493-21-3 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-[3-[4-[(3-chloro-4-fluorophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]-1,1-dimethyl-2-propynyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



IT **451492-95-8P 451492-96-9P 451492-99-2P**
451493-01-9P 451493-03-1P 451493-04-2P
451493-06-4P 451493-07-5P 451493-08-6P
451493-09-7P 451493-10-0P 451493-11-1P
451493-12-2P 451493-14-4P 451493-15-5P
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451493-31-5P 451493-32-6P 451493-33-7P
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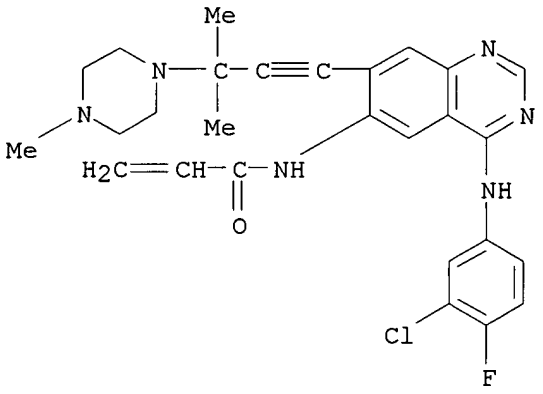
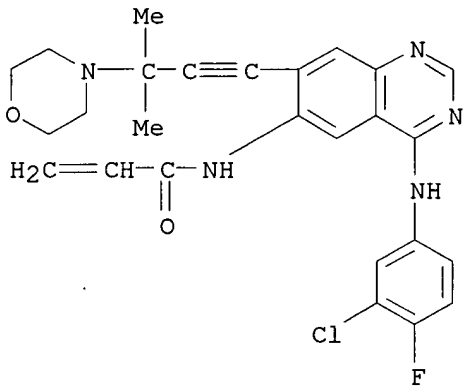
451494-20-5P 451494-21-6P 451494-25-0P
451494-29-4P 451495-11-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of phenylaminoquinazoline derivs. as inhibitors of tyrosine-specific protein kinase for prepn. and/or treatment of cancers, diseases caused by arteriosclerosis, or psoriasis)

RN 451492-95-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

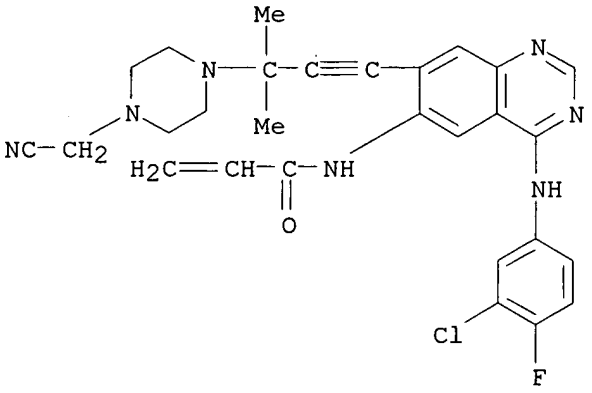


RN 451492-96-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-morpholinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 451492-99-2 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[4-(cyanomethyl)-1-piperazinyl]-3-methyl-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



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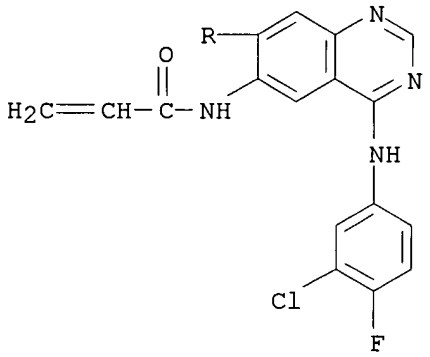
PAGE 1-A



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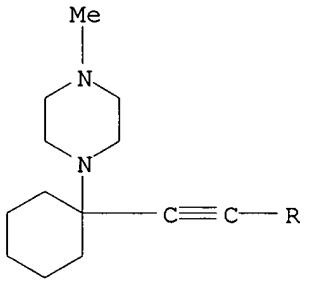

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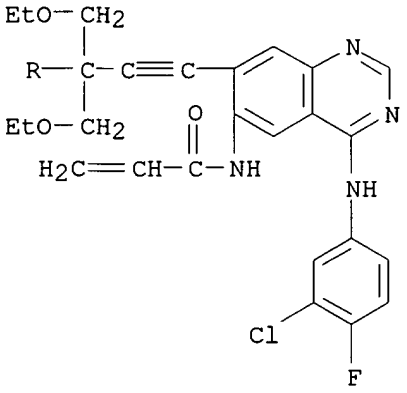
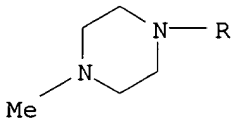
(9CI) (CA INDEX NAME)





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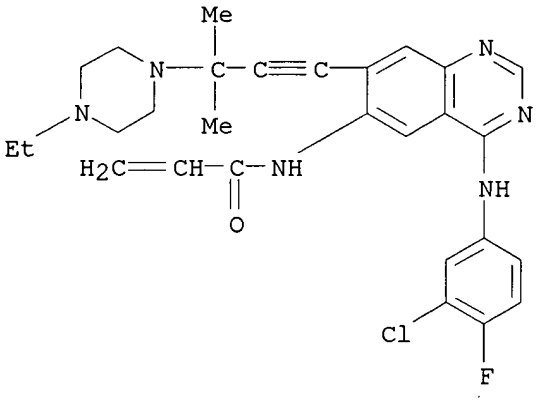

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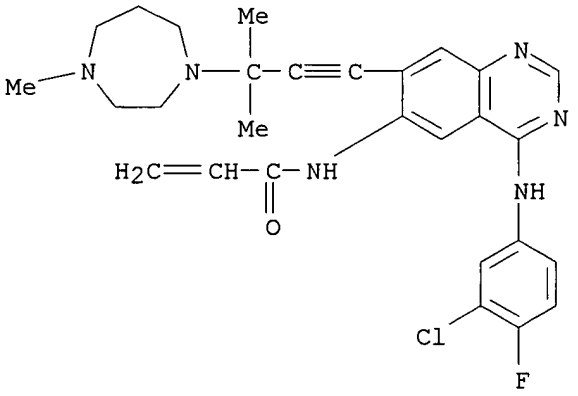

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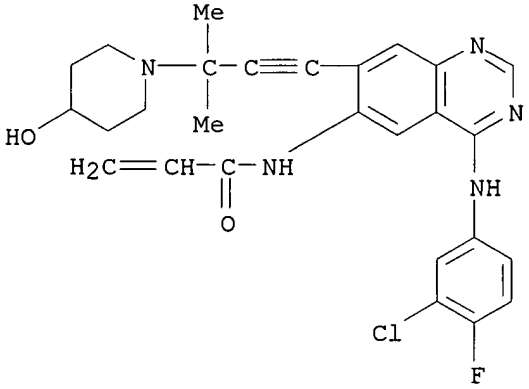

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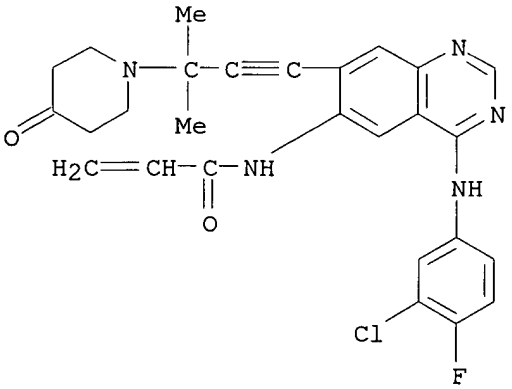

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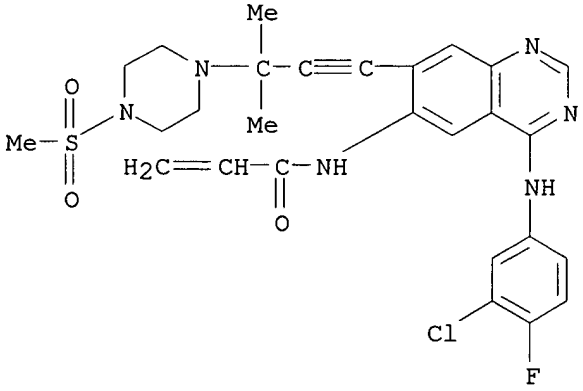

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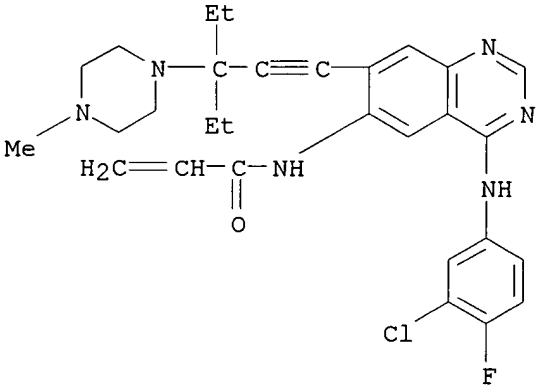

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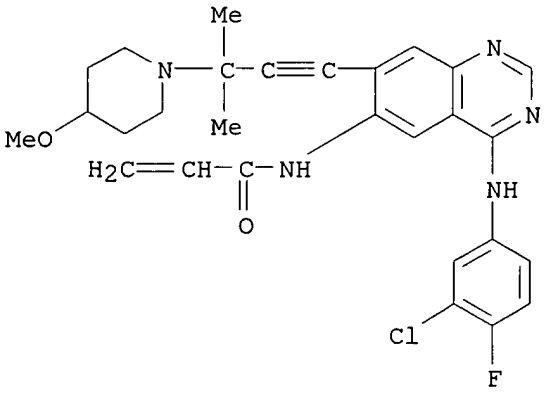

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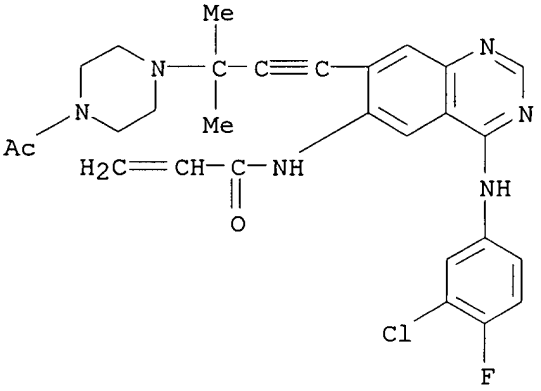

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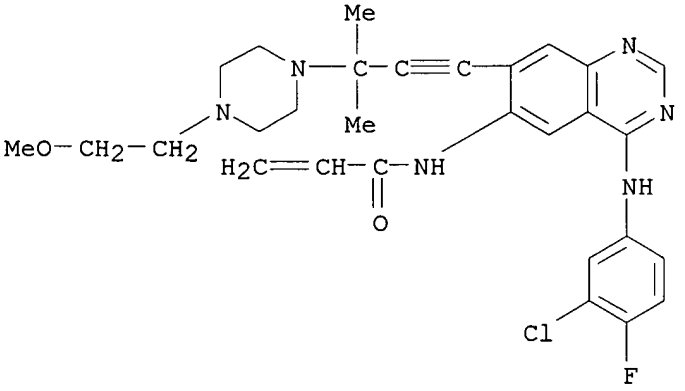

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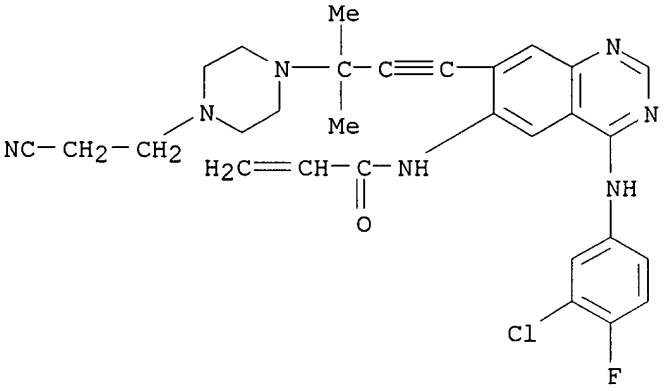

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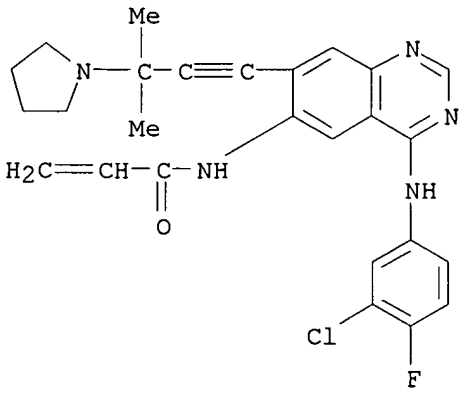
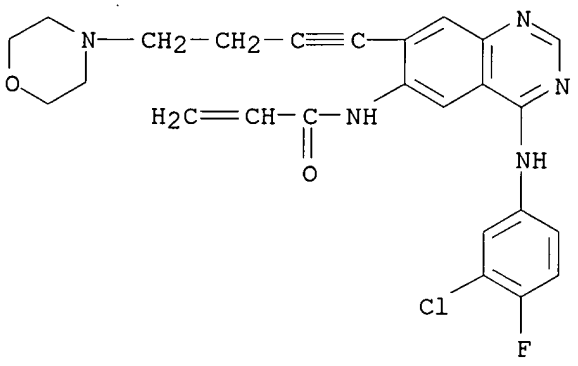
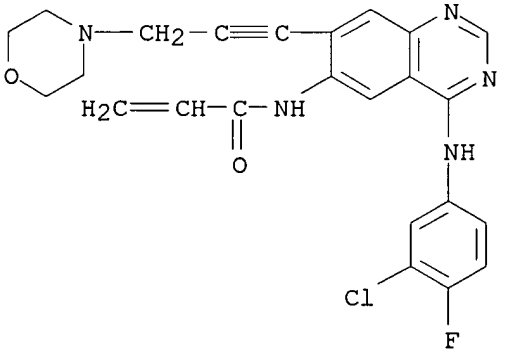
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(1-pyrrolidinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



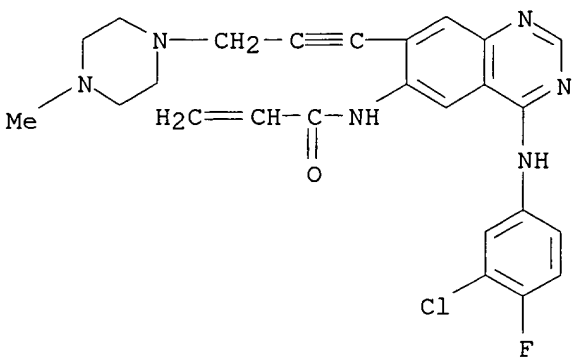
RN 451493-18-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-(4-morpholinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



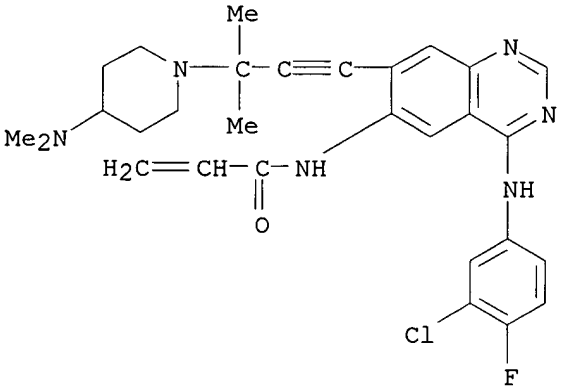
RN 451493-19-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)-1-propynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



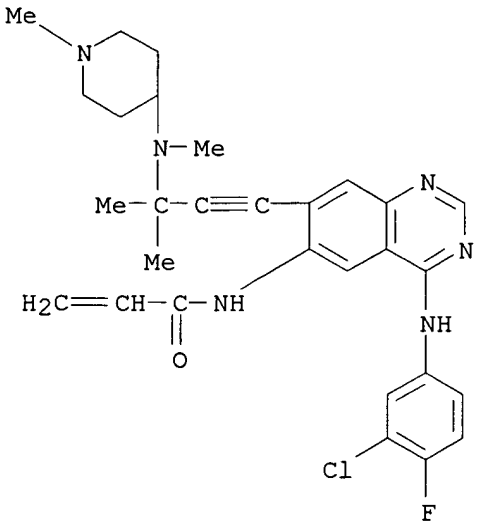
RN 451493-20-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-methyl-1-piperazinyl)-1-propynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



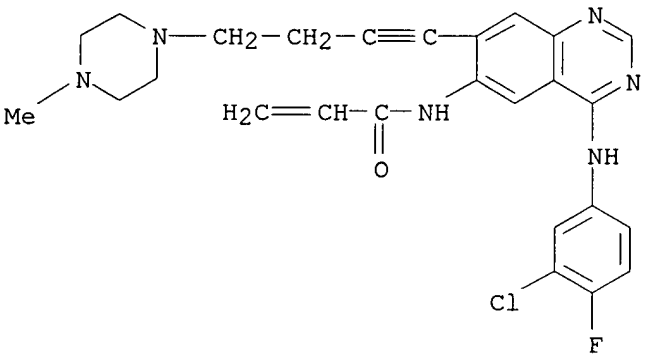
RN 451493-22-4 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[4-(dimethylamino)-1-piperidinyl]-3-methyl-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 451493-25-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-[methyl(1-methyl-4-piperidinyl)amino]-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

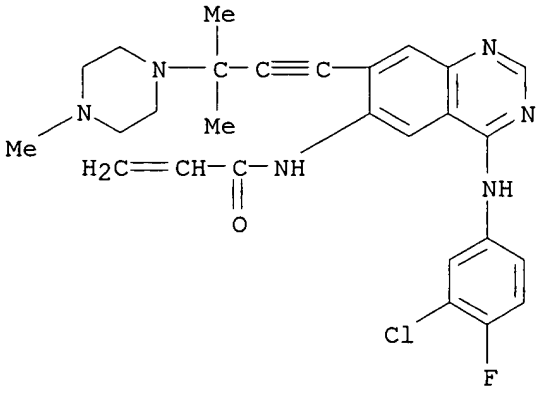


RN 451493-28-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



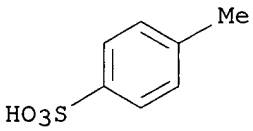
RN 451493-29-1 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(1Z)-3-methyl-3-(4-methyl-1-piperazinyl)-1-butenyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

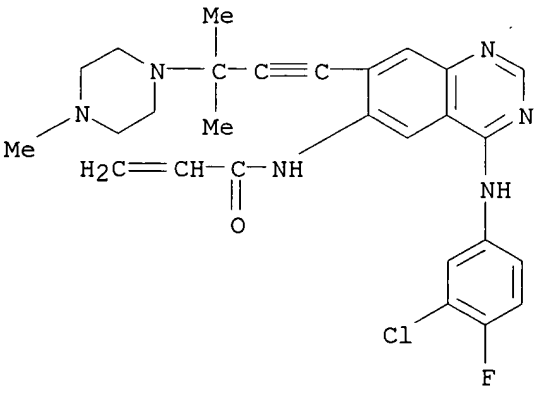


CM 2

CRN 104-15-4
CMF C7 H8 O3 S



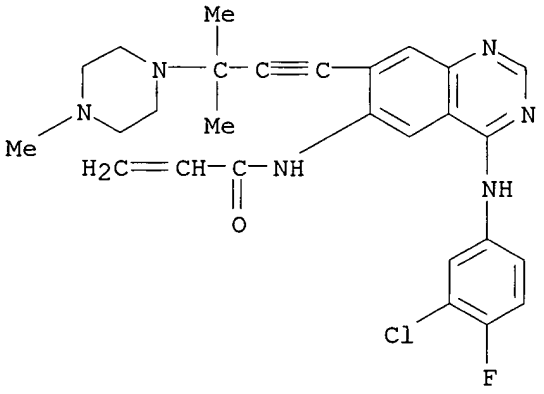
RN 451493-32-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, trihydrochloride (9CI) (CA INDEX NAME)



3 HCl

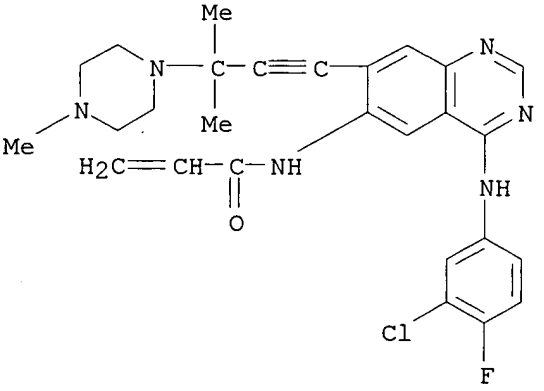
RN 451493-33-7 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

RN 451493-34-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, monohydrochloride (9CI) (CA INDEX NAME)

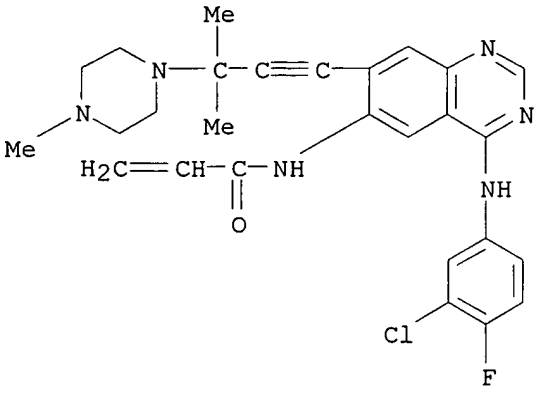


● HCl

RN 451493-35-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, dimethanesulfonate (9CI) (CA INDEX NAME)

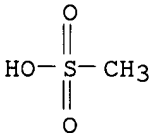
CM 1

CRN 451492-95-8
CMF C27 H28 Cl F N6 O



CM 2

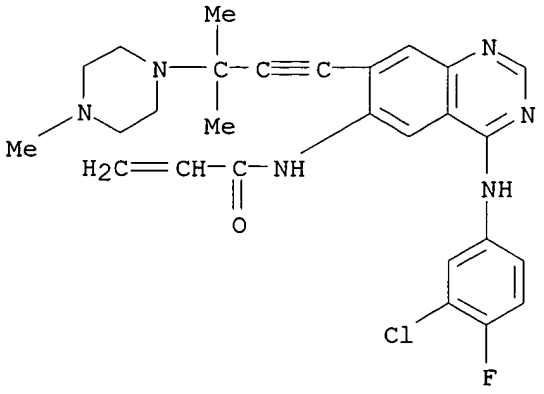
CRN 75-75-2
CMF C H4 O3 S



RN 451493-36-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, mono(4-methylbenzenesulfonate) (9CI) (CA INDEX NAME)

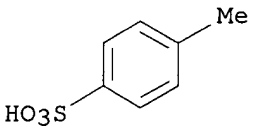
CM 1

CRN 451492-95-8
CMF C27 H28 Cl F N6 O



CM 2

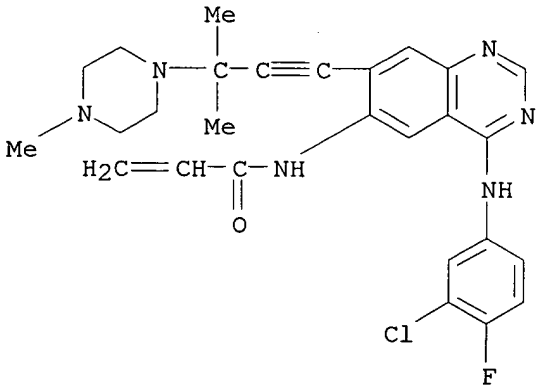
CRN 104-15-4
CMF C7 H8 O3 S



RN 451493-37-1 CAPLUS
CN 1,2-Ethanedisulfonic acid, compd. with N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-2-propenamide (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 451492-95-8
CMF C27 H28 Cl F N6 O



CM 2

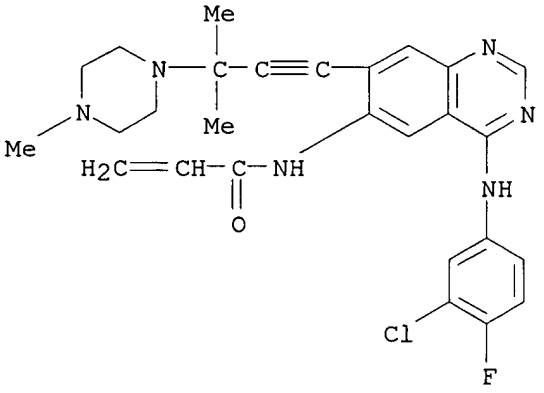
CRN 110-04-3
CMF C2 H6 O6 S2

$HO_3S-CH_2-CH_2-SO_3H$

RN 451493-38-2 CAPLUS
CN 1,2-Ethanedisulfonic acid, compd. with N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-2-propenamide (2:1) (9CI) (CA INDEX NAME)

CM 1

CRN 451492-95-8
CMF C27 H28 Cl F N6 O



CM 2

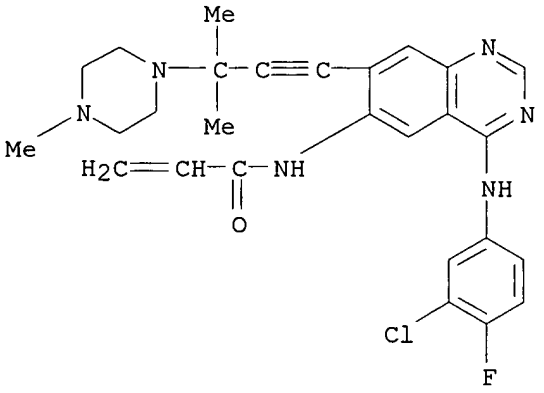
CRN 110-04-3
CMF C2 H6 O6 S2

$HO_3S-CH_2-CH_2-SO_3H$

RN 451493-39-3 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, dibenzenesulfonate (9CI) (CA INDEX NAME)

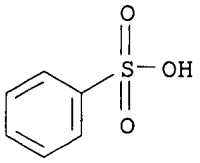
CM 1

CRN 451492-95-8
CMF C27 H28 Cl F N6 O



CM 2

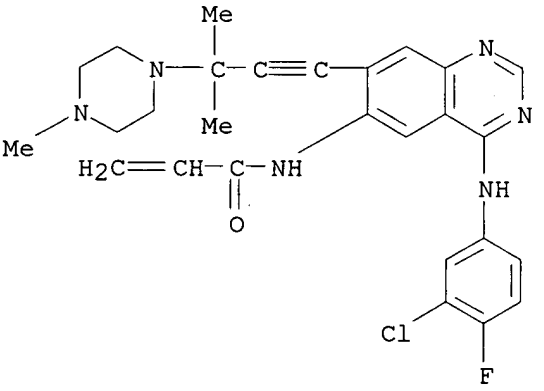
CRN 98-11-3
CMF C6 H6 O3 S



RN 451493-40-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, sulfate (1:1) (9CI) (CA INDEX NAME)

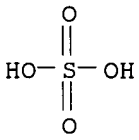
CM 1

CRN 451492-95-8
CMF C27 H28 Cl F N6 O



CM 2

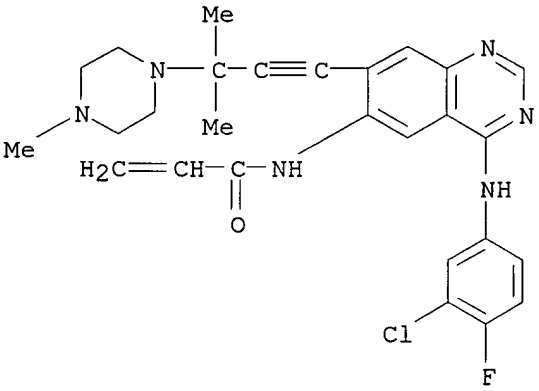
CRN 7664-93-9
CMF H2 O4 S



RN 451493-41-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, sulfate (2:3) (9CI) (CA INDEX NAME)

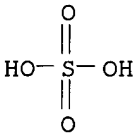
CM 1

CRN 451492-95-8
CMF C27 H28 Cl F N6 O



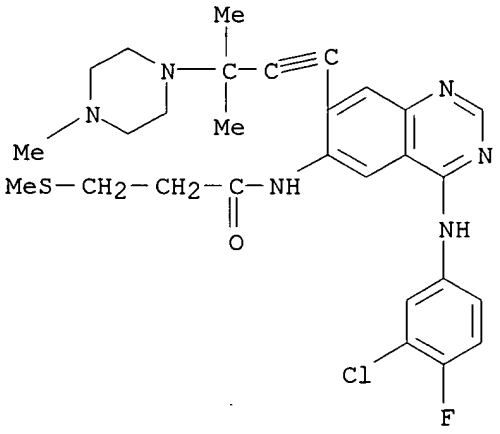
CM 2

CRN 7664-93-9
CMF H2 O4 S

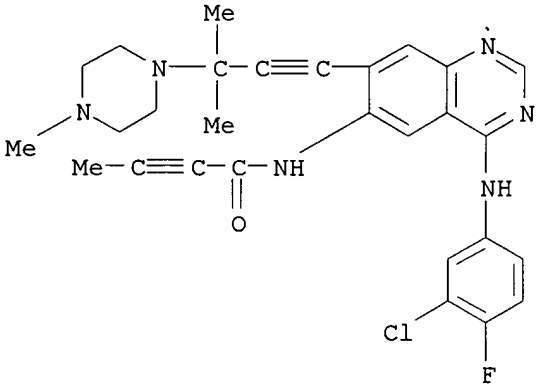


RN 451493-64-4 CAPLUS
CN Propanamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-3-(methylthio)- (9CI) (CA INDEX

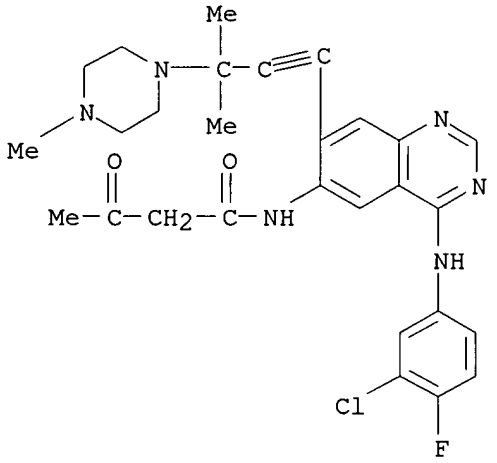
NAME)



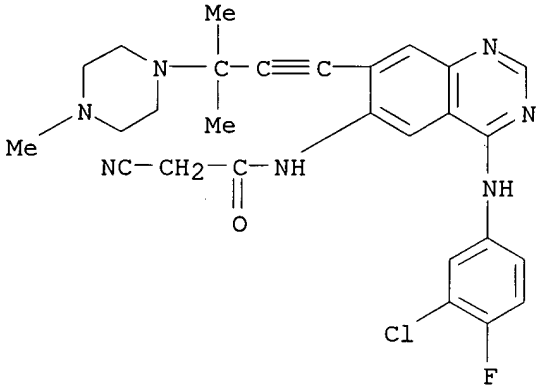
RN 451493-65-5 CAPLUS
CN 2-Butynamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



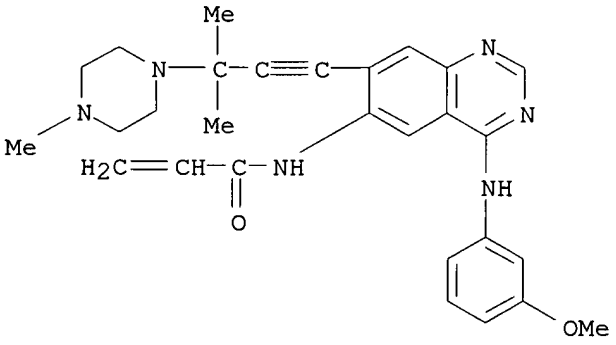
RN 451493-66-6 CAPLUS
CN Butanamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-3-oxo- (9CI) (CA INDEX NAME)



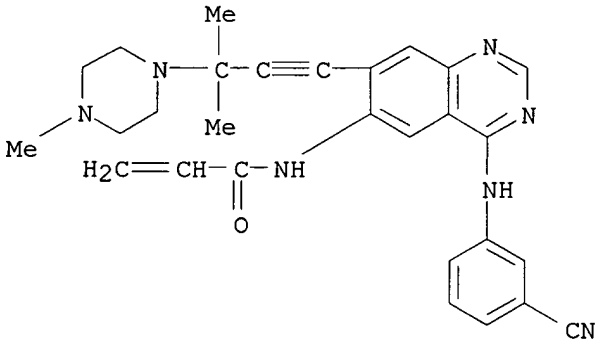
RN 451493-67-7 CAPLUS
CN Acetamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-2-cyano- (9CI) (CA INDEX NAME)



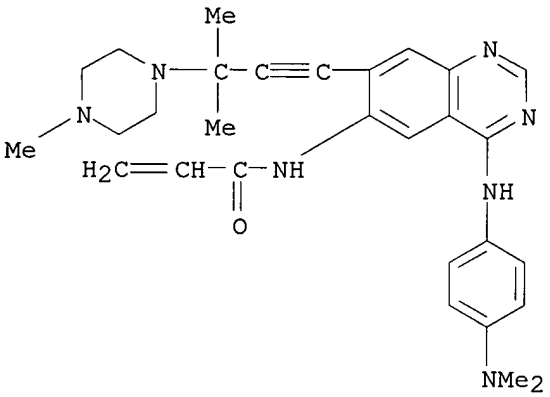
RN 451493-69-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-methoxyphenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



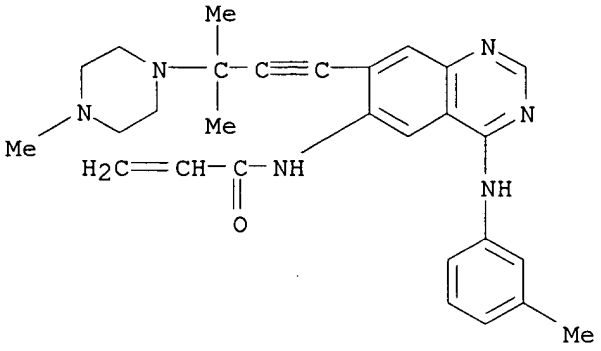
RN 451493-70-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-cyanophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



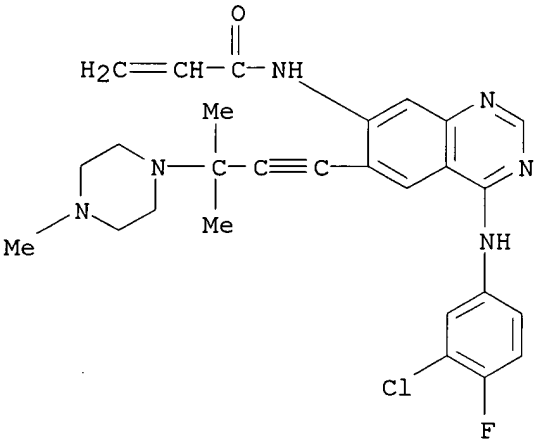
RN 451493-71-3 CAPLUS
CN 2-Propenamide, N-[4-[[4-(dimethylamino)phenyl]amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 451493-72-4 CAPLUS
CN 2-Propenamide, N-[7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-4-[(3-methylphenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

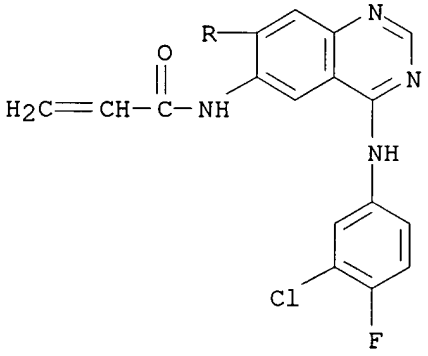


RN 451494-16-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-6-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-7-quinazolinyl]- (9CI) (CA INDEX NAME)

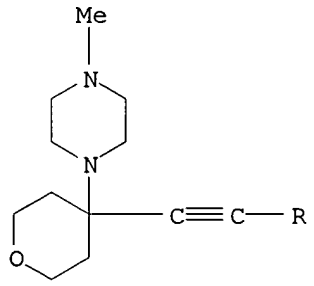


RN 451494-18-1 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[tetrahydro-4-(4-methyl-1-piperazinyl)-2H-pyran-4-yl]ethynyl]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



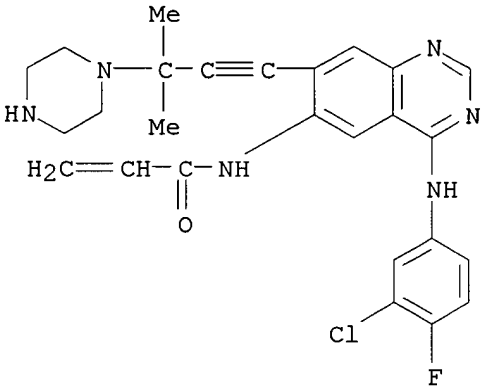
PAGE 2-A



RN 451494-20-5 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, trifluoroacetate (9CI) (CA INDEX NAME)

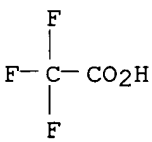
CM 1

CRN 451494-19-2
CMF C26 H26 Cl F N6 O



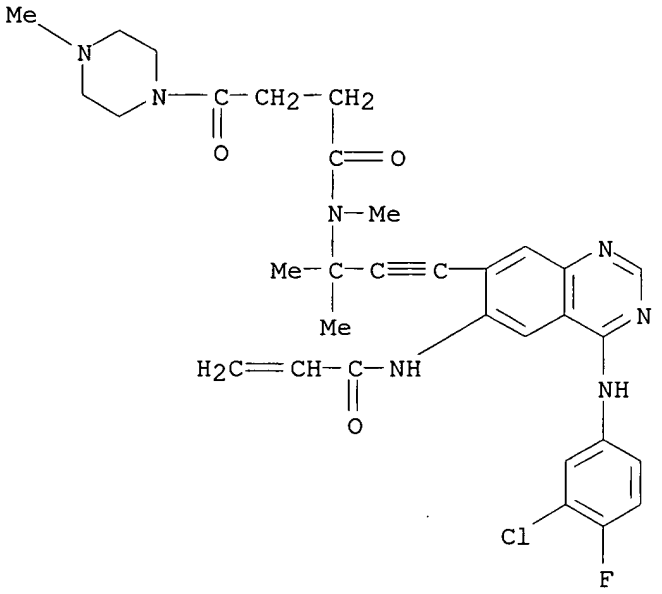
CM 2

CRN 76-05-1
CMF C2 H F3 O2



RN 451494-21-6 CAPLUS
CN 1-Piperazinebutanamide, N-[3-[4-[(3-chloro-4-fluorophenyl)amino]-6-[(1-oxo-

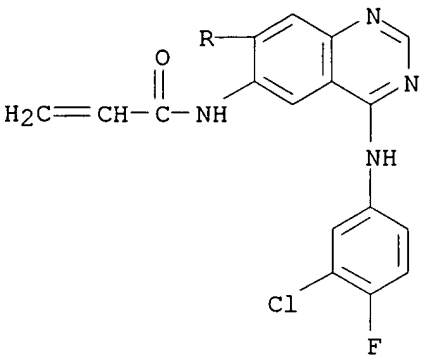
2-propenyl)amino]-7-quinazolinyl]-1,1-dimethyl-2-propynyl]-N,4-dimethyl-.gamma.-oxo- (9CI) (CA INDEX NAME)

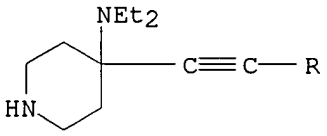


RN 451494-25-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[4-(diethylamino)-4-piperidinyl]ethynyl]-6-quinazolinyl]-, tris(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

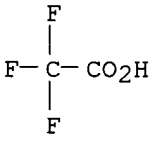
CRN 451494-24-9
CMF C28 H30 Cl F N6 O



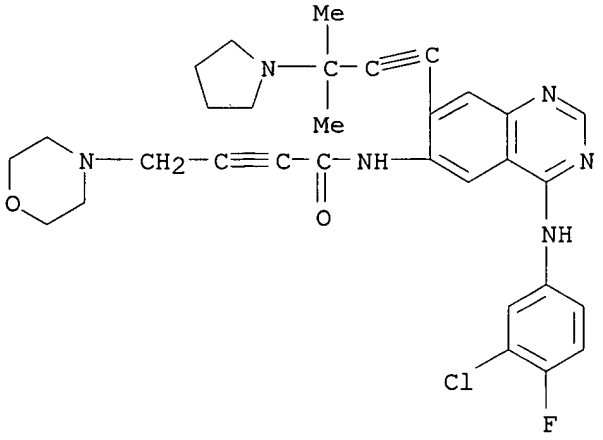


CM 2

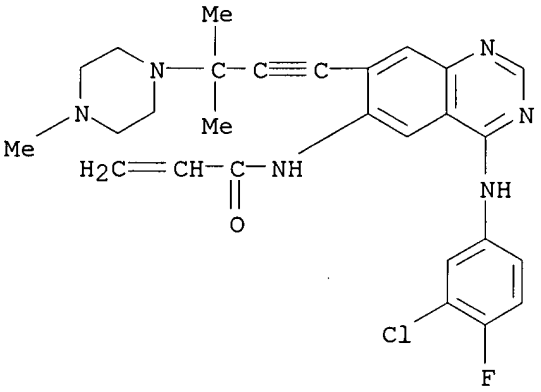
CRN 76-05-1
CMF C2 H F3 O2



RN 451494-29-4 CAPLUS
CN 2-Butynamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(1-pyrrolidinyl)-1-butynyl]-6-quinazolinyl]-4-(4-morpholinyl)- (9CI) (CA INDEX NAME)

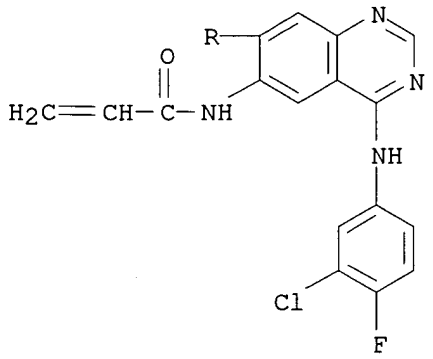


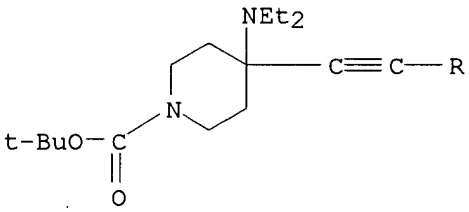
RN 451495-11-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butynyl]-6-quinazolinyl]-, hydrate (9CI) (CA INDEX NAME)



●x H_2O

IT **451494-23-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of phenylaminoquinazoline derivs. as inhibitors of tyrosine-specific protein kinase for prepn. and/or treatment of cancers, diseases caused by arteriosclerosis, or psoriasis)
RN 451494-23-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[4-[(3-chloro-4-fluorophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]ethynyl]-4-(diethylamino)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



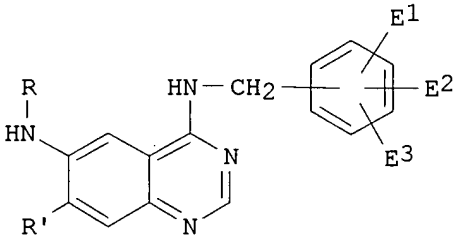


RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:610316 CAPLUS
DN 137:163829
TI Use of a composition comprising a retinoid and an Erb inhibitor in the preparation of a medicament for the treatment of retinoid skin damage
IN Elder, James Tilford; Varani, James
PA Warner-Lambert Company, USA
SO Eur. Pat. Appl., 43 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1230919	A2	20020814	EP 2002-2611	20020205
	EP 1230919	A3	20021218		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	AU 2002015470	A5	20020815	AU 2002-15470	20020207
	CN 1370535	A	20020925	CN 2002-104570	20020208
	US 2002169176	A1	20021114	US 2002-73569	20020211
	JP 2002275095	A2	20020925	JP 2002-33608	20020212
PRAI	US 2001-268220P	P	20010212		

OS MARPAT 137:163829
GI

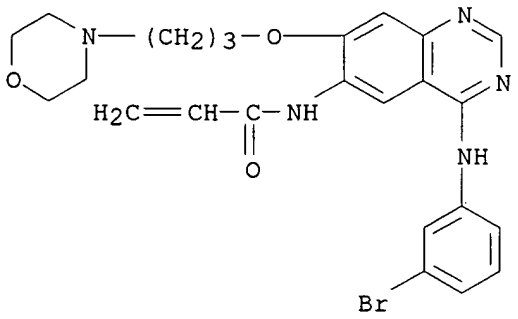


I

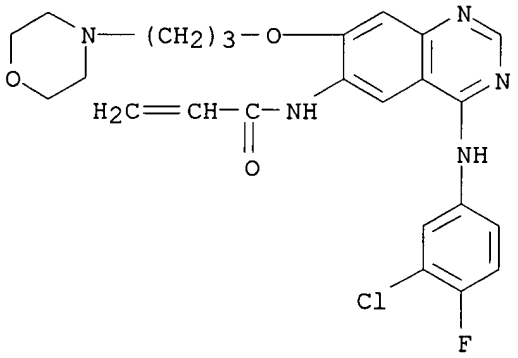
AB Erb inhibitors used in combination with retinoids are effective to prevent skin injury otherwise caused by retinoids alone. A method of treating skin aging and similar skin disorders comprises administering retinoids in combination with erb inhibitors I (E1-E3 include halo; R is alkylcarbonyl or alkenylcarbonyl; R' is lower alkoxy optionally substituted with amino groups).

IT **198959-99-8 267243-28-7 289499-45-2**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(retinoid and Erb inhibitor for treatment of retinoid skin damage)

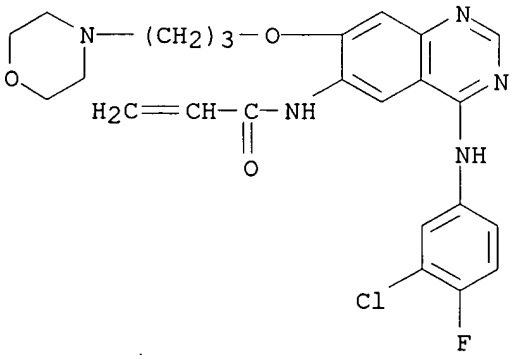
RN 198959-99-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)

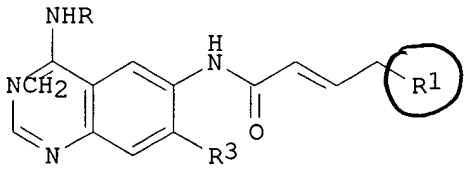


2 HCl

L7 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:487536 CAPLUS
DN 137:63250
TI Quinazoline derivatives as inhibitors of human EFG tyrosine kinase
IN Himmelsbach, Frank; Langkopf, Elke; Blech, Stefan; Jung, Birgit; Baum, Elke; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002050043	A1	20020627	WO 2001-EP14569	20011212
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE 10063435	A1	20020704	DE 2000-10063435	20001220
	AU 2002019174	A5	20020701	AU 2002-19174	20011212
	US 2002173509	A1	20021121	US 2001-23099	20011217
PRAI	DE 2000-10063435	A	20001220		
	US 2000-259201P	P	20001228		
	WO 2001-EP14569	W	20011212		

OS MARPAT 137:63250
GI



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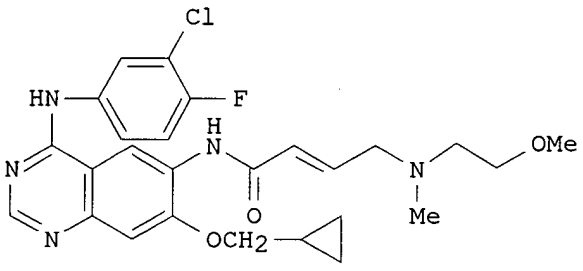


II

AB Quinazoline derivs. I [R = PhCH2, PhCHMe, 3,4-Cl(F)C6H3; R1 = NMeR2, NEt2, NEtCH2CH2OMe, N(CH2CH2OMe)2, morpholino; R2 = Me, Et, CHMe2, cyclopropyl,

CH2CH2OMe, 3-tetrahydrofuryl, 2-tetrahydrofurylmethyl, 3-tetrahydrofurylmethyl, 4-tetrahydropyranyl, 4-tetrahydropyranylmethyl; R3 = cyclopropylmethoxy, cyclobutyloxy, cyclopentyloxy, 3-tetrahydrofuranyloxy, 2-tetrahydrofuranylmethoxy, 3-tetrahydrofuranylmethoxy, 4-tetrahydropyranyloxy, 4-tetrahydropyranylmethoxy] were prepd. for use as inhibitors of signal transduction caused by human EFG receptor tyrosine kinase. They are useful in the treatment of tumoral diseases, diseases of the lung and the respiratory tract, the gastrointestinal tract, and the gallbladder and bile ducts. Thus, the quinazoline II was prepd. by converting bromocrotonic acid to its chloride, and reaction with 4-[(3-chloro-4-fluorophenyl)amino]-6-amino-7-cyclopropylmethoxyquinazoline, followed by MeNHCH2CH2OMe. II had an IC50 against human EFG receptor kinase of 0.7 nM.

IT **439081-18-2P 439081-40-0P 439081-41-1P 439081-42-2P**

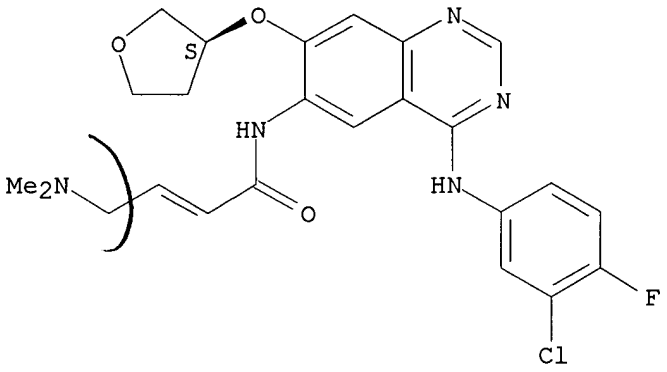
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of quinazoline derivs. as inhibitors of human EFG tyrosine kinase)

RN 439081-18-2 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)

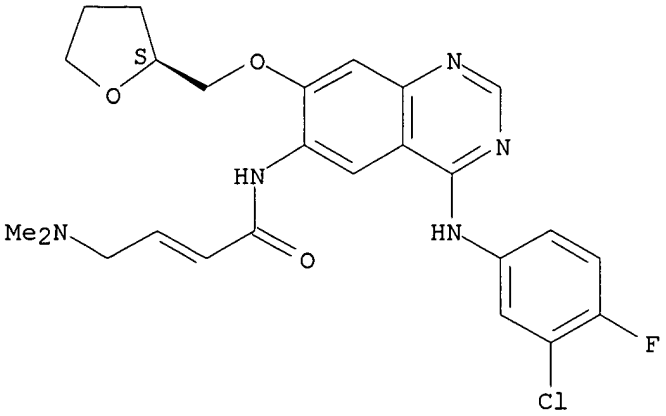
Absolute stereochemistry.
Double bond geometry unknown.



RN 439081-40-0 CAPLUS

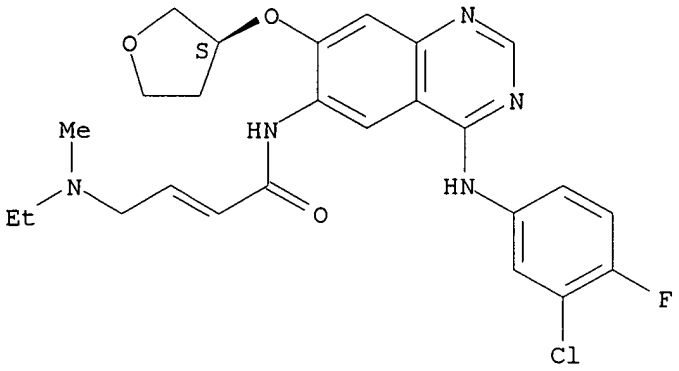
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(2S)-tetrahydro-2-furanyl]methoxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



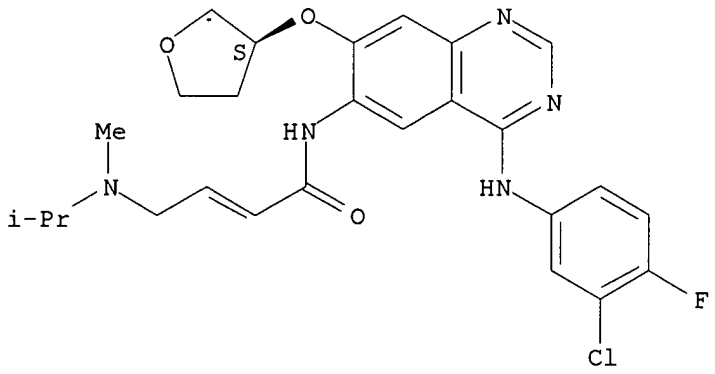
RN 439081-41-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(ethylmethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 439081-42-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-[methyl(1-methylethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

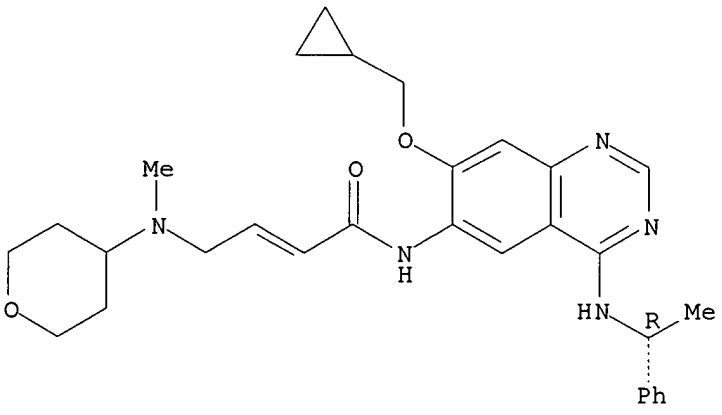


IT **439081-14-8P 439081-15-9P 439081-16-0P**
439081-17-1P 439081-19-3P 439081-20-6P
439081-21-7P 439081-22-8P 439081-24-0P
439081-25-1P 439081-27-3P 439081-28-4P
439081-32-0P 439081-33-1P 439081-34-2P
439081-35-3P 439081-36-4P 439081-37-5P
439081-38-6P 439081-39-7P 439081-43-3P
439081-45-5P 439081-46-6P 439081-47-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazoline derivs. as inhibitors of human EFG tyrosine kinase)

RN 439081-14-8 CAPLUS

CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[methyl(tetrahydro-2H-pyran-4-yl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

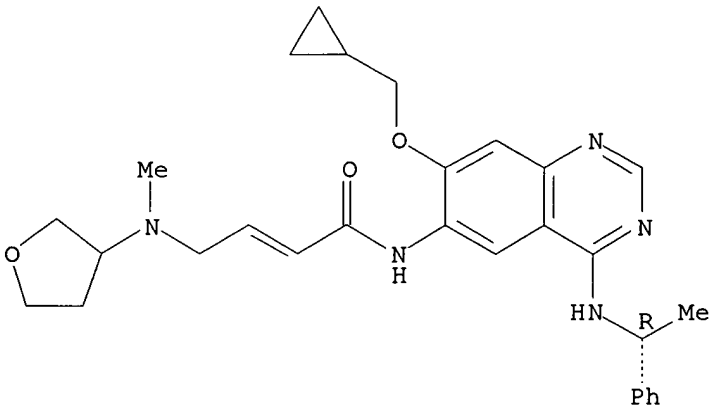


RN 439081-15-9 CAPLUS

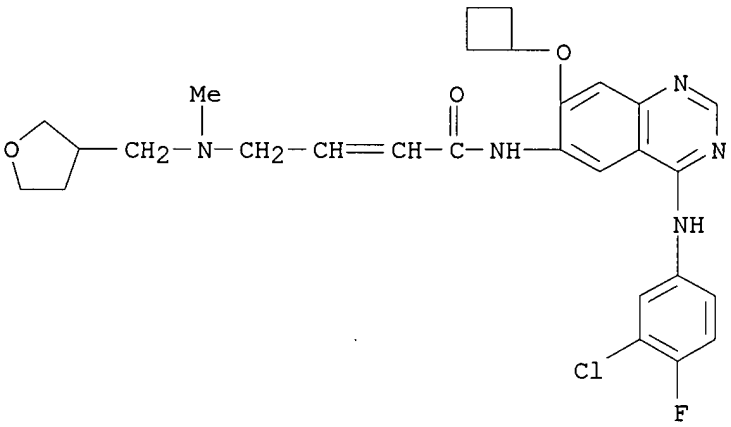
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[methyl(tetrahydro-3-furanyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

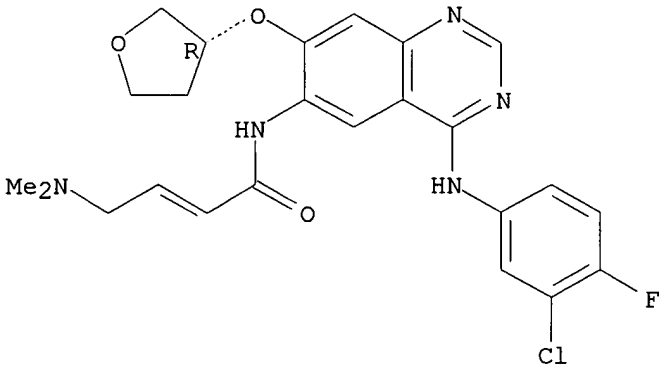


RN 439081-16-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]-4-[methyl[(tetrahydro-3-furanyl)methyl]amino]- (9CI) (CA INDEX NAME)

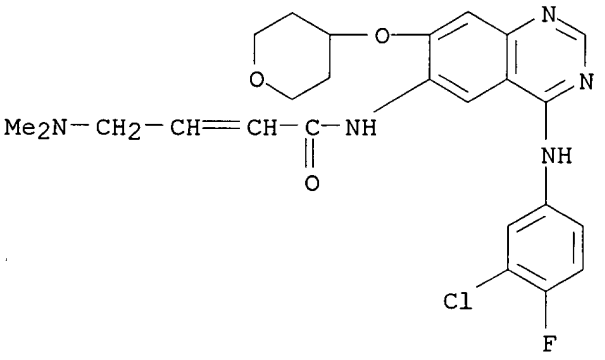


RN 439081-17-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3R)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)

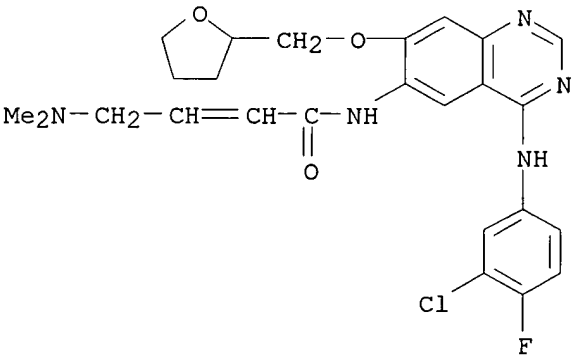
Absolute stereochemistry.
Double bond geometry unknown.



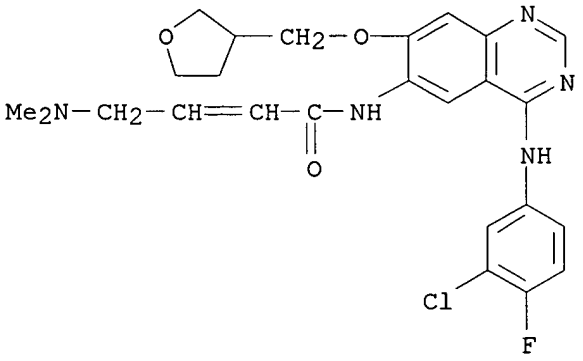
RN 439081-19-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)oxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



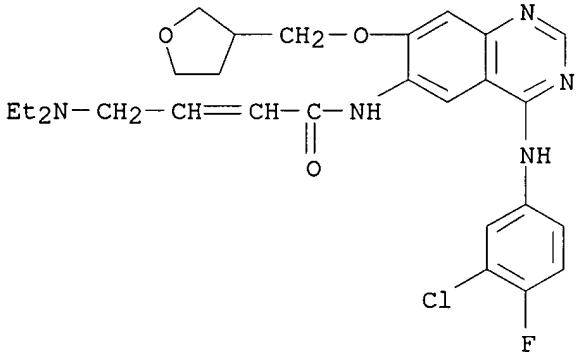
RN 439081-20-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2-furanyl)methoxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



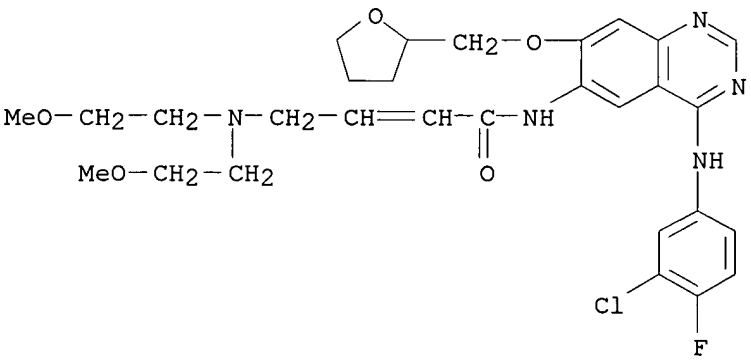
RN 439081-21-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-3-furanyl)methoxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



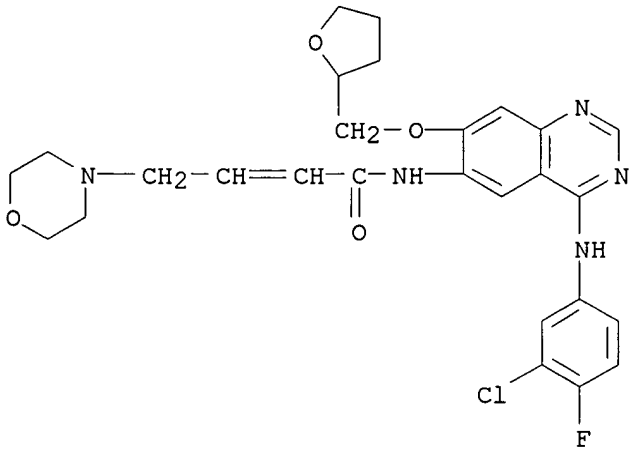
RN 439081-22-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-3-furanyl)methoxy]-6-quinazolinyl]-4-(diethylamino)- (9CI) (CA INDEX NAME)



RN 439081-24-0 CAPLUS
CN 2-Butenamide, 4-[bis(2-methoxyethyl)amino]-N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2-furanyl)methoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

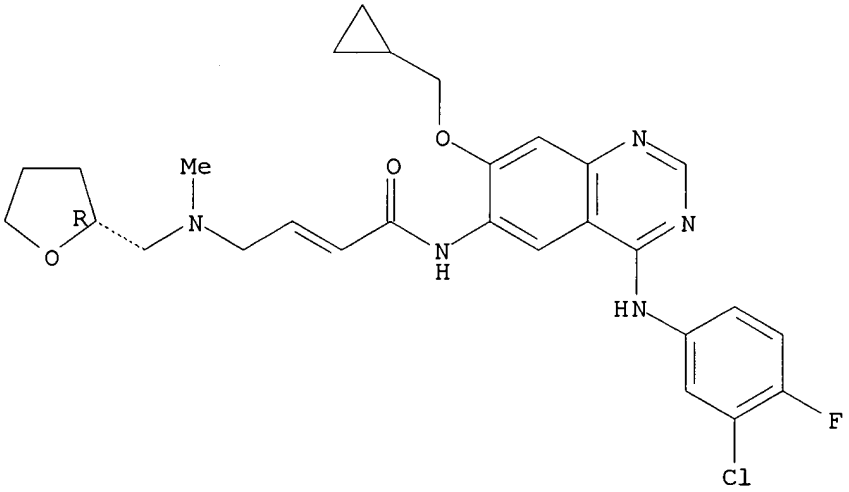


RN 439081-25-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2-furanyl)methoxy]-6-quinazolinyl]-4-(4-morpholinyl)- (9CI) (CA INDEX NAME)



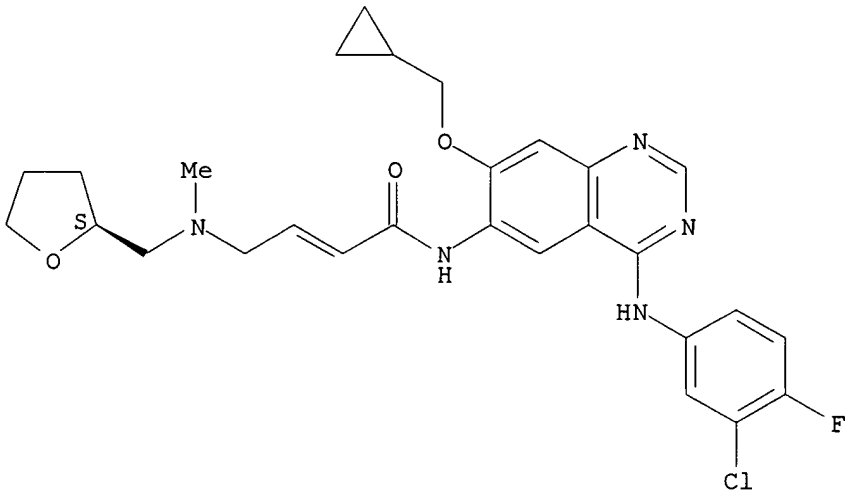
RN 439081-27-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[[(2R)-tetrahydro-2-furanyl]methyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

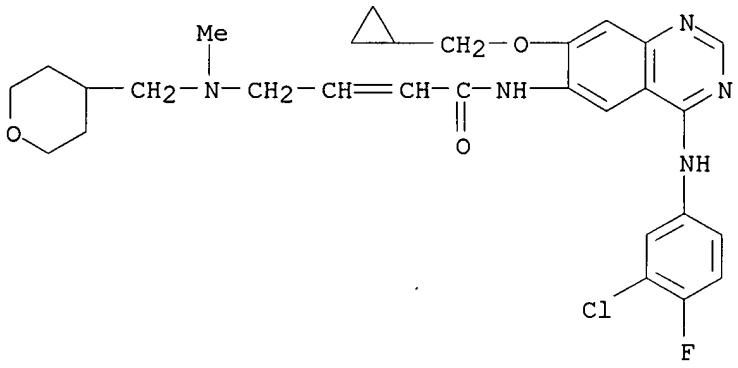


RN 439081-28-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[[(2S)-tetrahydro-2-furanyl]methyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

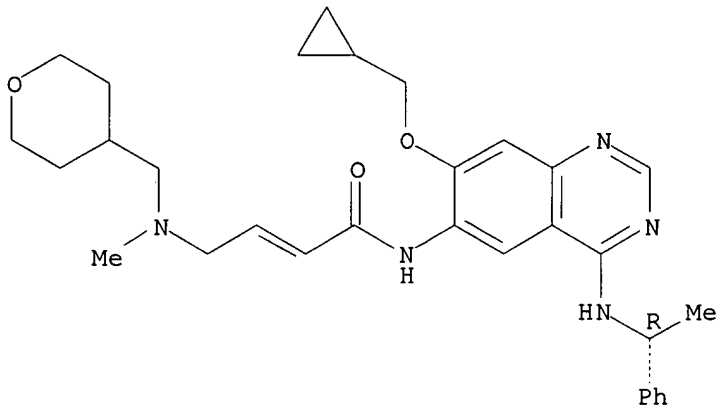


RN 439081-32-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[(tetrahydro-2H-pyran-4-yl)methyl]amino]- (9CI) (CA INDEX NAME)



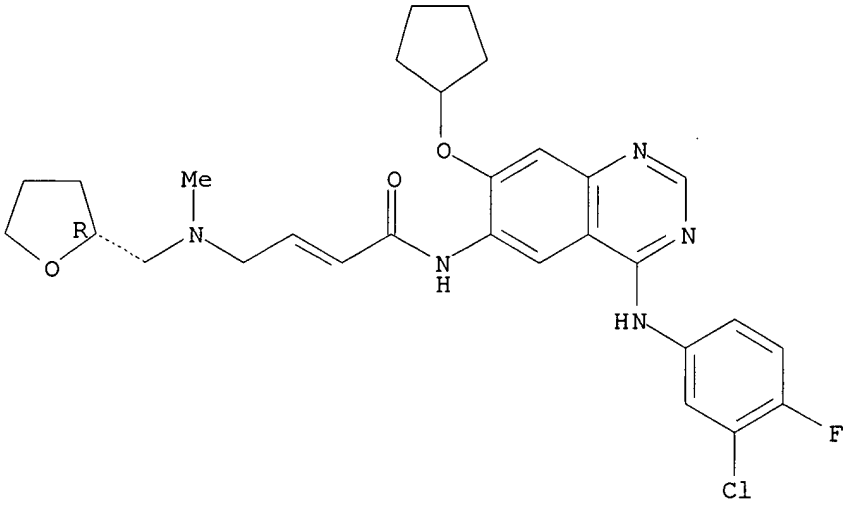
RN 439081-33-1 CAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[methyl[(tetrahydro-2H-pyran-4-yl)methyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



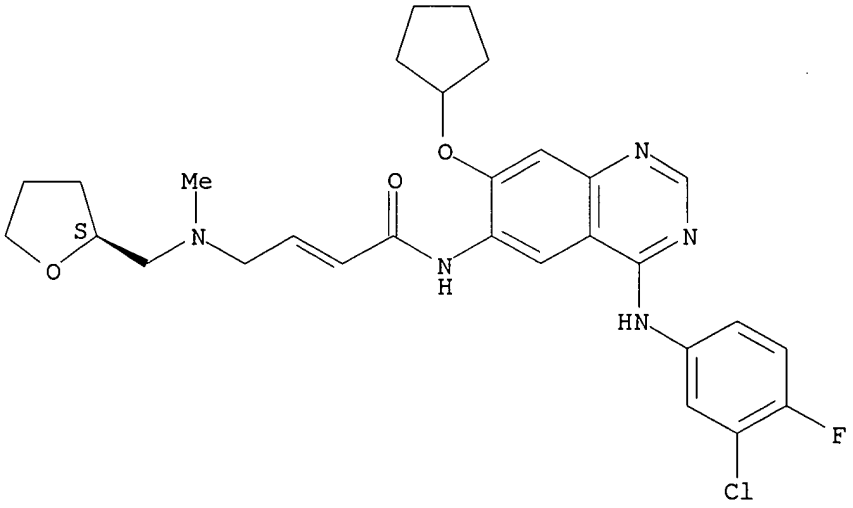
RN 439081-34-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]-4-[methyl[[(2R)-tetrahydro-2-furanyl]methyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

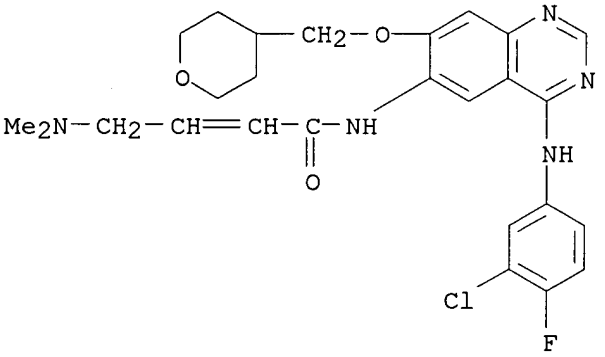


RN 439081-35-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]-4-[methyl[[(2S)-tetrahydro-2-furanyl]methyl]amino]- (9CI) (CA INDEX NAME)

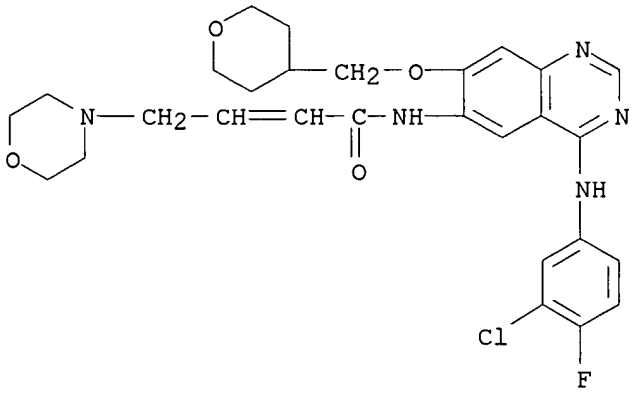
Absolute stereochemistry.
Double bond geometry unknown.



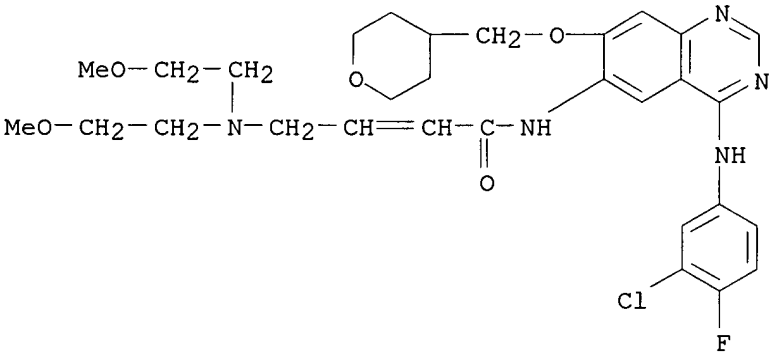
RN 439081-36-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)methoxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)



RN 439081-37-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)methoxy]-6-quinazolinyl]-4-(4-morpholinyl)- (9CI) (CA INDEX NAME)

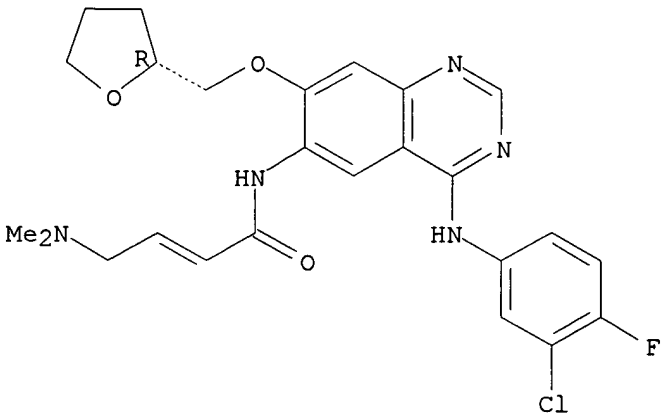


RN 439081-38-6 CAPLUS
CN 2-Butenamide, 4-[bis(2-methoxyethyl)amino]-N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)methoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



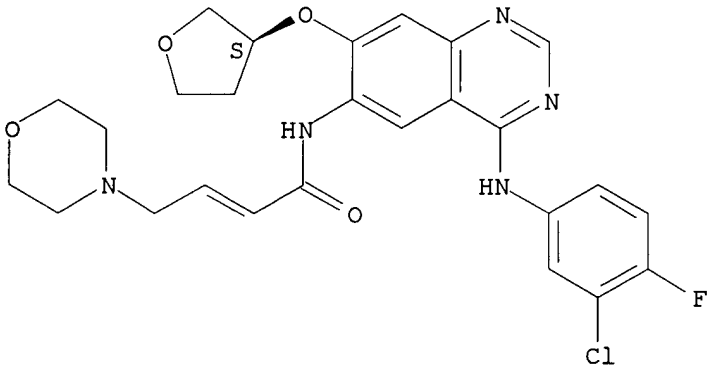
RN 439081-39-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(2R)-tetrahydro-2-furanyl]methoxy]-6-quinazolinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



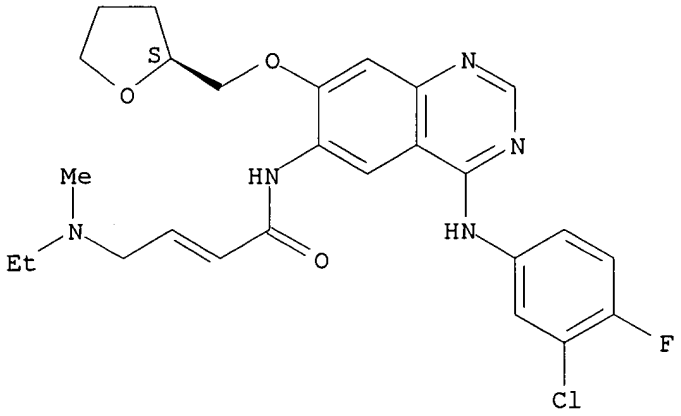
RN 439081-43-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



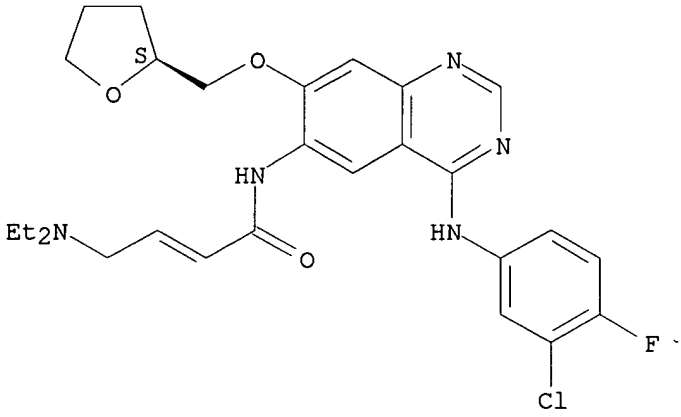
RN 439081-45-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(2S)-tetrahydro-2-furanyl]methoxy]-6-quinazolinyl]-4-(ethylmethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



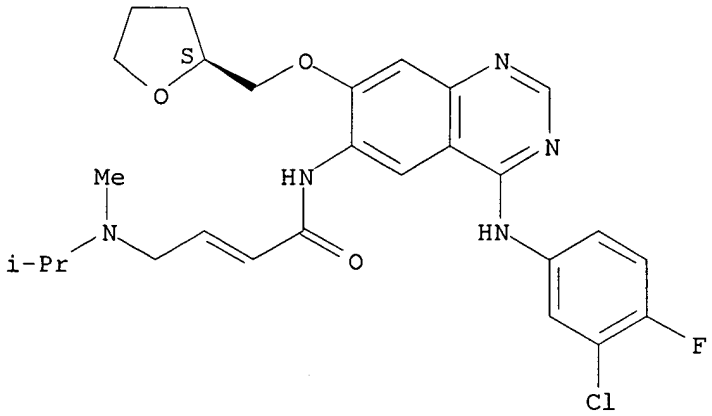
RN 439081-46-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(2S)-tetrahydro-2-furanyl]methoxy]-6-quinazolinyl]-4-(diethylamino)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 439081-47-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(2S)-tetrahydro-2-furanyl]methoxy]-6-quinazolinyl]-4-[methyl(1-methylethyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

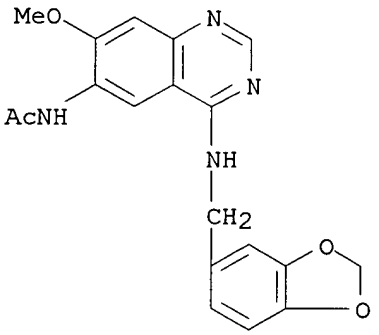
L17 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:314395 CAPLUS
DN 136:335540
TI Use of PDE V inhibitors for improved fecundity in mammals
IN Westbrook, Simon Lempriere; Zanzinger, Johannes Friedrich
PA Pfizer Limited, UK; Pfizer Inc.
SO Eur. Pat. Appl., 20 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 1199070	A2	20020424	EP 2001-308684	20011011
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2003018036	A1	20030123	US 2001-982445	20011018
	US 6548508	B2	20030415		
	JP 2002220346	A2	20020809	JP 2001-322195	20011019
	US 2003018037	A1	20030123	US 2002-229534	20020827
PRAI	GB 2000-25782	A	20001020		
	US 2000-253338P	P	20001128		
	US 2001-982445	A1	20011018		

AB The invention relates to the use of a cyclic guanosine 3',5'-monophosphate phosphodiesterase type five (cGMP PDE V) inhibitor for increasing fecundity in a mammal by one or more of (a) promoting the growth of an oocyte, zygote, blastocyst, embryo and/or fetus, (b) increasing the rate or probability of survival of an embryo and/or fetus and (c) increasing the birth wt. of a progeny, or for increasing milk productivity. I.v. and tablet formulations are exemplified. Formulations and packs contg. the PDE V inhibitors for pharmaceutical or veterinary use are claimed.

IT **150450-69-4**
RL: AGR (Agricultural use); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of PDE V inhibitors for improved fecundity in mammals)

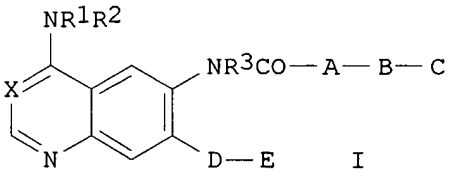
RN 150450-69-4 CAPLUS
CN Acetamide, N-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-7-methoxy-6-quinazolinyl]- (9CI) (CA INDEX NAME)



L7 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:171892 CAPLUS
DN 136:216762
TI Preparation of 4-amino-6-heterocyclylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018376	A1	20020307	WO 2001-EP9536	20010818
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE 10042062	A1	20020307	DE 2000-10042062	20000826
	AU 2001095482	A5	20020313	AU 2001-95482	20010818
	US 2002115675	A1	20020822	US 2001-934631	20010822
PRAI	DE 2000-10042062	A	20000826		
	US 2000-230542P	P	20000905		
	WO 2001-EP9536	W	20010818		

OS MARPAT 136:216762
GI



I

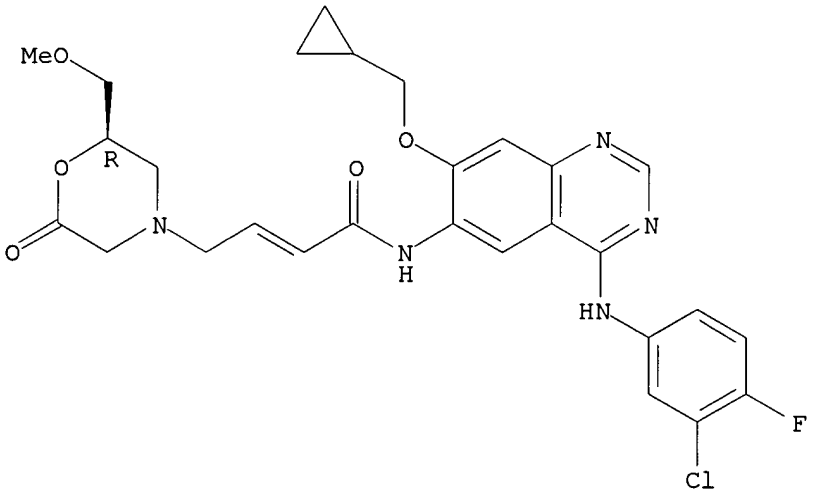
AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = (substituted) alkenyl, alkenylcarbonyl, etc.; C = (substituted) 2-oxomorpholin-4-yl, etc; D = oxyalkenyl, O; E = (substituted) amino, alkenylimino, imidazolyl, cycloalkyl; or DE = H, (substituted) alkoxy, etc.], were prepd. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(ethoxycarbonylmethyl)-N-((R)-2-hydroxy-3-methoxypropyl)amino]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) and MeSO2OH in MeCN were stirred for 4 h under reflux to give 69% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[(R)-2-methoxymethyl-6-oxomorpholin-4-yl]-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 2 nM. The invention relates to the use of the title compds.

for treating tumor diseases, and lung and respiratory tract disorders.

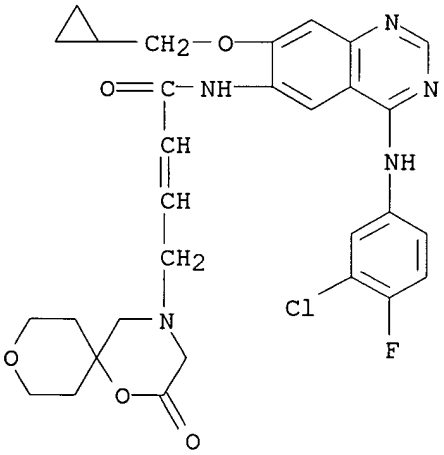
IT **402569-98-6P 402569-99-7P 402570-00-7P 402570-01-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402569-98-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2R)-2-(methoxymethyl)-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

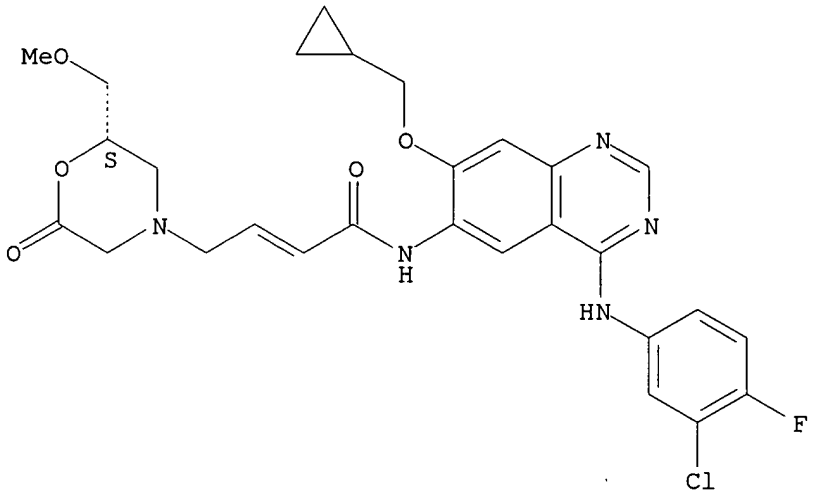


RN 402569-99-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2-oxo-1,9-dioxa-4-azaspiro[5.5]undec-4-yl)- (9CI) (CA INDEX NAME)

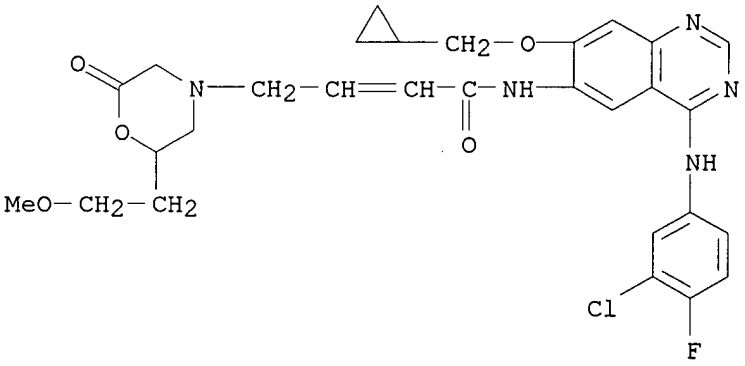


RN 402570-00-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2S)-2-(methoxymethyl)-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

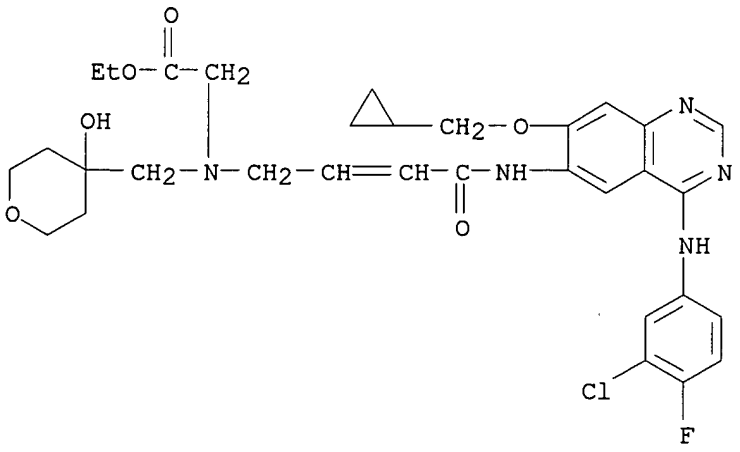
Absolute stereochemistry.
Double bond geometry unknown.



RN 402570-01-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[2-(2-methoxyethyl)-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)



IT **402569-89-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)
RN 402569-89-5 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(tetrahydro-4-hydroxy-2H-pyran-4-yl)methyl]-, ethyl ester (9CI) (CA INDEX NAME)

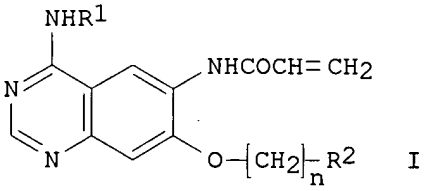


RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:171891 CAPLUS
DN 136:216761
TI Preparation of 4-amino-6-vinylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018375	A1	20020307	WO 2001-EP9534	20010818
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE 10042064	A1	20020307	DE 2000-10042064	20000826
	AU 2002010444	A5	20020313	AU 2002-10444	20010818
	US 6403580	B1	20020611	US 2001-935498	20010823
PRAI	DE 2000-10042064	A	20000826		
	US 2000-230541P	P	20000905		
	WO 2001-EP9534	W	20010818		

OS MARPAT 136:216761
GI



I

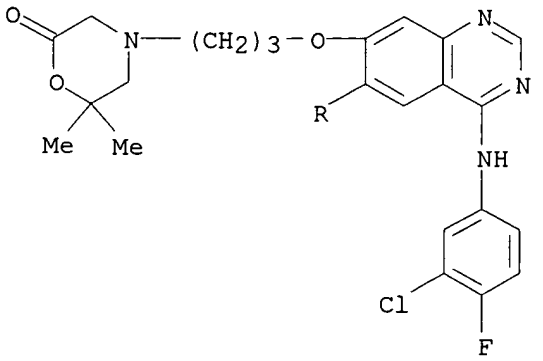
AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-(2-oxotetrahydrofuran-4-yl)methylamino, N(CH2CO2R3)2, (substituted) R4OCOCH2NCH2CH2OH, 2-oxomorpholin-4-yl; R3 = H, Me, Et; R4 = H, alkyl; n = 2-4],were prepd. Thus, a mixt. of CH2:CHCO2H and Et3N was stirred for 1 h at -50.degree. with CH2:CHCO2Cl in THF followed by addn. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propyloxy]quinazoline (prepn. given) in THF at -55.degree. and slowly heating up at 0.degree. up to completely conversion to give 60% 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxomorpholin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. One of the exemplified examples, 4-[(R)-(1-phenylethyl)amino]-7-[2-(2,2-dimethyl-

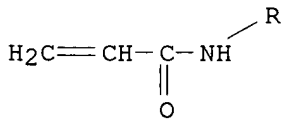
6-oxomorpholin-4-yl)ethoxy]-6-[(vinylcarbonyl)amino]quinazoline, inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.4 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402724-01-0P 402724-02-1P 402724-03-2P**
402724-05-4P 402724-09-8P 402724-10-1P
402724-11-2P 402724-12-3P 402724-14-5P
402724-15-6P 402724-16-7P 402724-17-8P
402724-18-9P 402724-19-0P 402724-20-3P
402724-21-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402724-01-0 CAPLUS

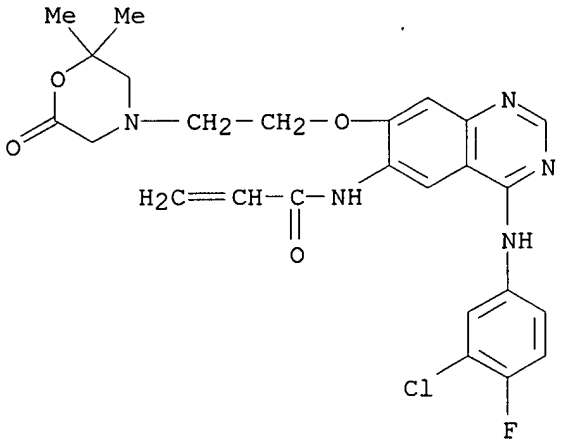
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(2,2-dimethyl-6-oxo-4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)





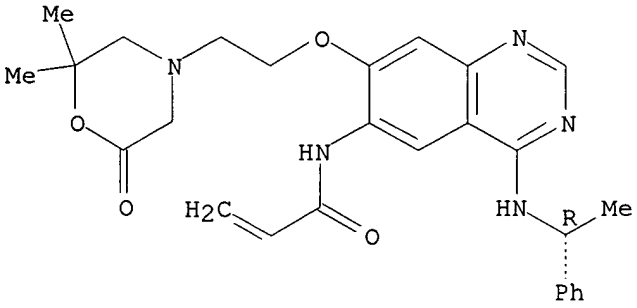
RN 402724-02-1 CAPLUS

CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-4-morpholinyl)ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



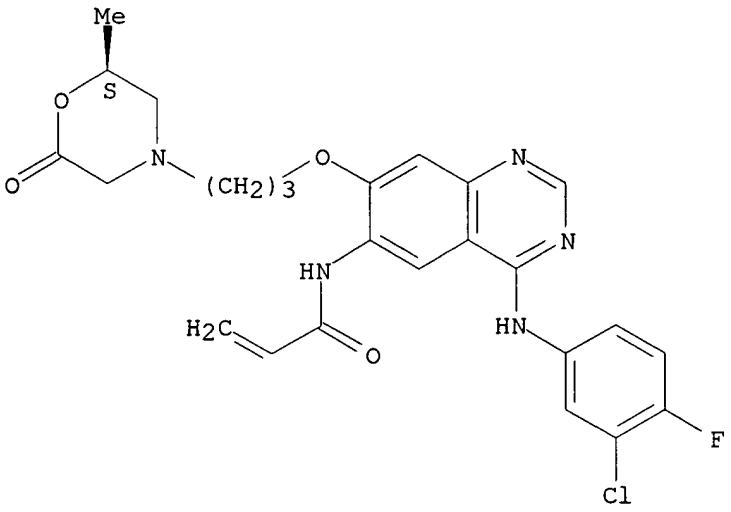
RN 402724-03-2 CAPLUS
CN 2-Propenamide, N-[7-[2-(2,2-dimethyl-6-oxo-4-morpholinyl)ethoxy]-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



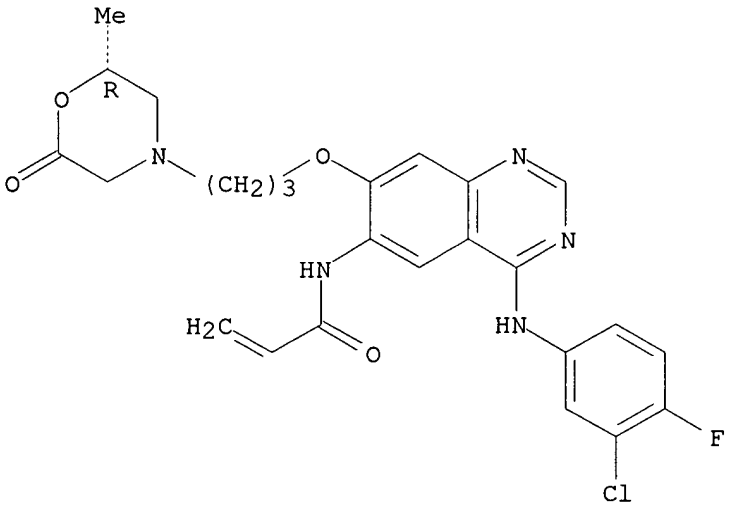
RN 402724-05-4 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[(2S)-2-methyl-6-oxo-4-morpholinyl]propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



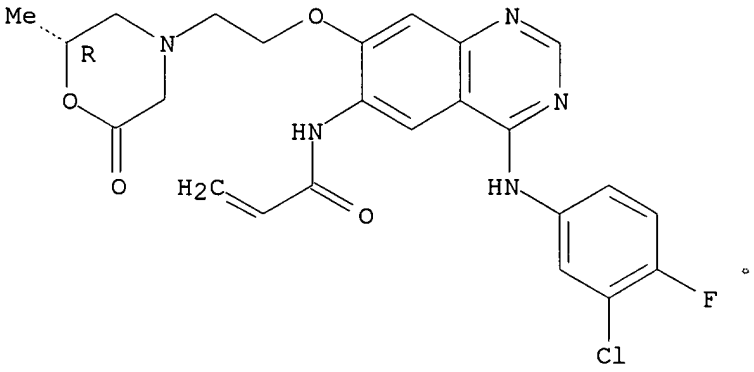
RN 402724-09-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[(2R)-2-methyl-6-oxo-4-morpholinyl]propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



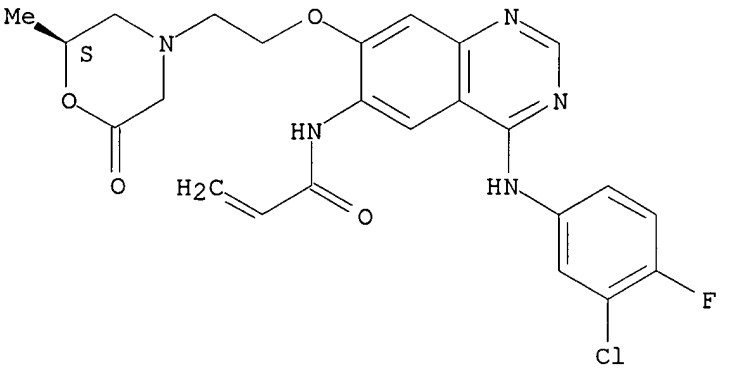
RN 402724-10-1 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-[(2R)-2-methyl-6-oxo-4-morpholinyl]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



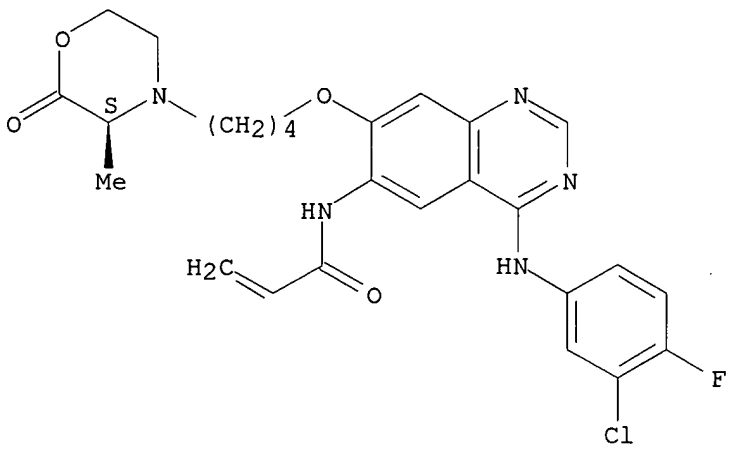
RN 402724-11-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-[(2S)-2-methyl-6-oxo-4-morpholinyl]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

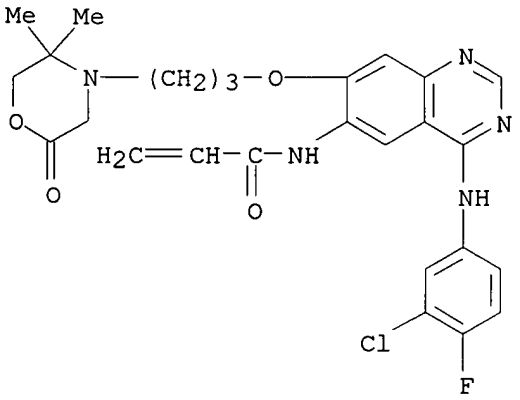


RN 402724-12-3 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-[(3S)-3-methyl-2-oxo-4-morpholinyl]butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

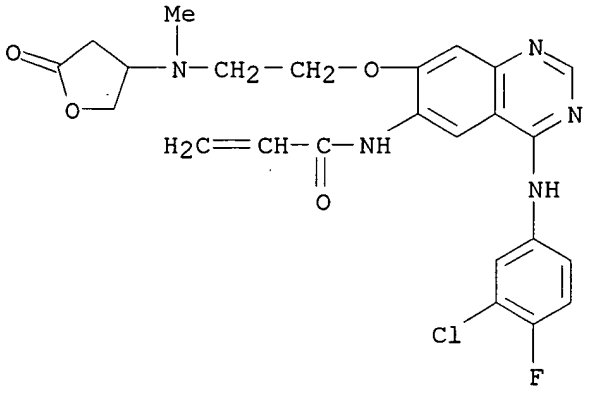
Absolute stereochemistry.



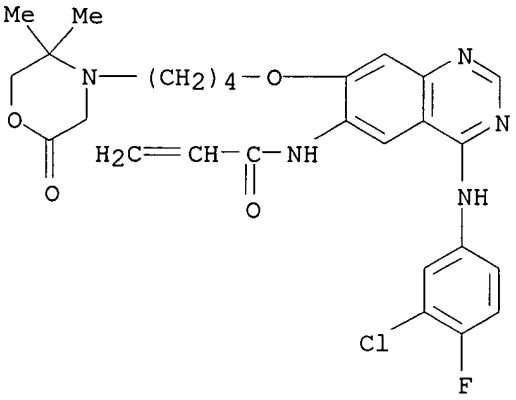
RN 402724-14-5 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(5,5-dimethyl-2-oxo-4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 402724-15-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-[methyl(tetrahydro-5-oxo-3-furanyl)amino]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

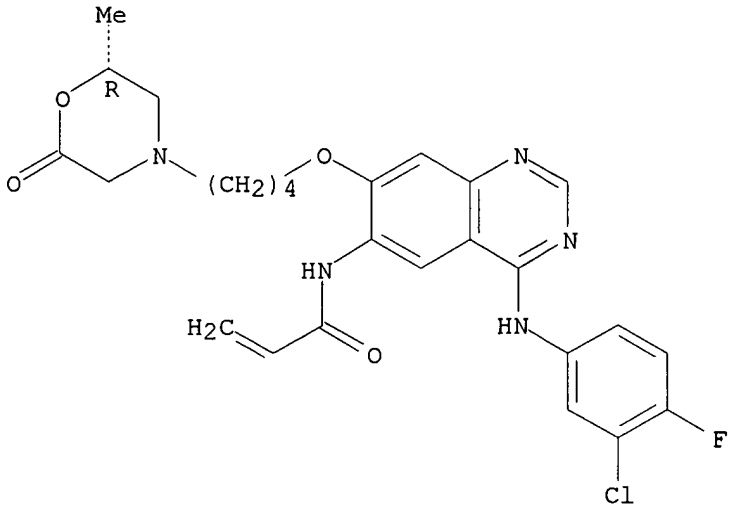


RN 402724-16-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-(5,5-dimethyl-2-oxo-4-morpholinyl)butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



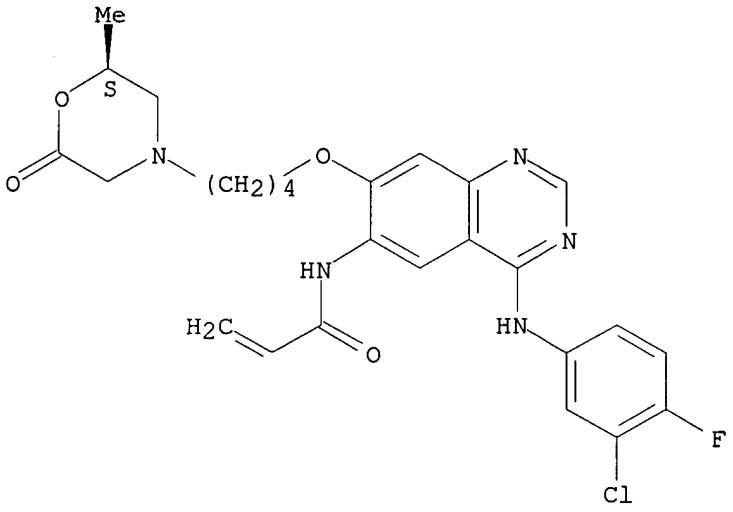
RN 402724-17-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-[(2R)-2-methyl-6-oxo-4-morpholinyl]butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

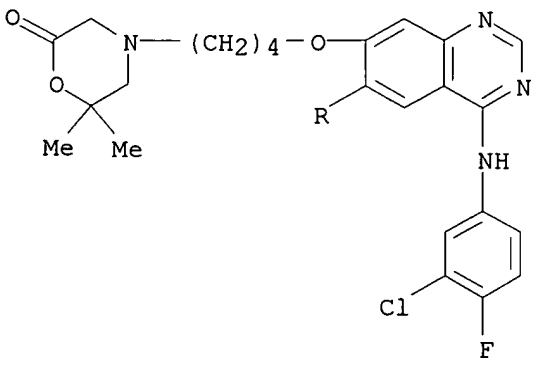


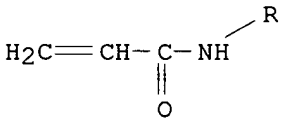
RN 402724-18-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-[(2S)-2-methyl-6-oxo-4-morpholinyl]butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

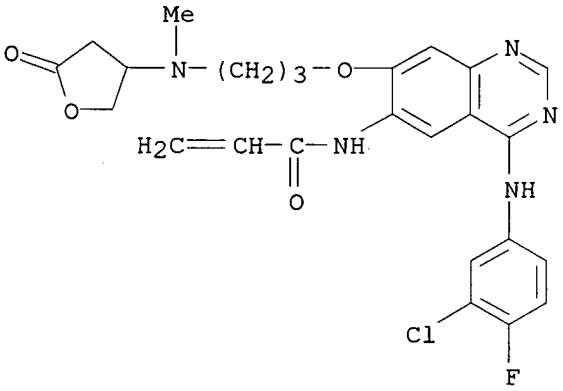


RN 402724-19-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-(2,2-dimethyl-6-oxo-4-morpholinyl)butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

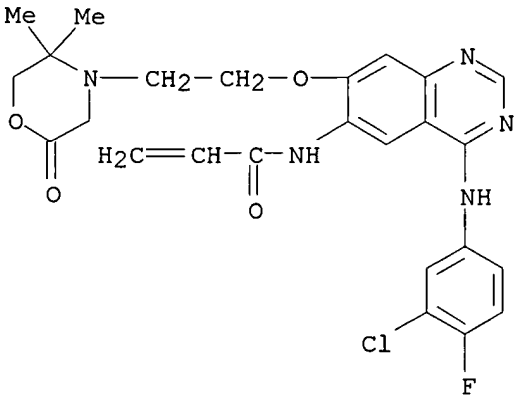




RN 402724-20-3 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[methyl(tetrahydro-5-oxo-3-furanyl)amino]propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 402724-21-4 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-(5,5-dimethyl-2-oxo-4-morpholinyl)ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:171889 CAPLUS
DN 136:232315
TI Preparation of 4-amino-6-vinylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002018373	A1	20020307	WO 2001-EP9537	20010818
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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DE 10042060	A1	20020307	DE 2000-10042060	20000826
US 2002077330	A1	20020620	US 2001-929931	20010815
AU 2001084021	A5	20020313	AU 2001-84021	20010818
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US 2000-230389P	P	20000906		
WO 2001-EP9537	W	20010818		

OS MARPAT 136:232315
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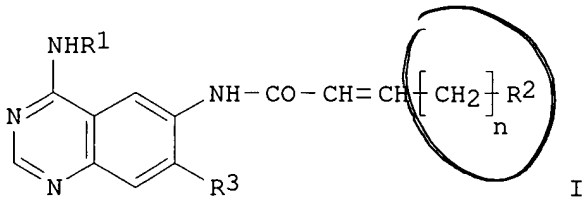


I

AB Title compds. [I; R1 = PhCH2, 1-phenylethyl, (substituted) Ph; R2 = N-[(1,3-dioxolan-2-yl)methyl]methylamino, (substituted) R4OCOCH2NCH2CH2OH, 2-oxomorpholin-4-yl; R4 = H, alkyl; R3 = H, (alkoxy)alkoxy, cycloalkylalkoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy; n = 1-3], were prepd. Thus, a mixt. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-cyclopropylmethoxyquinazoline (prepn. given) and disopropylethylamine in THF was dropwise treated under ice-cooling with BrCH2CH:CHCO2Cl (prepn. given) in CH2Cl2 followed by stirring for 1 h under ice-cooling and for 2 h at room temp. and addn. of (S)-(2-hydroxypropylamino)acetic acid tert-Bu ester in CH2Cl2 to give after stirring over night at room temp. and stirring for 5 h at 60.degree. 64% 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-[N-(tert-butyloxycarbonylmethyl)-N-((S)-2-hydroxyprop-1-yl)amino]-1-oxo-2-buten-1-

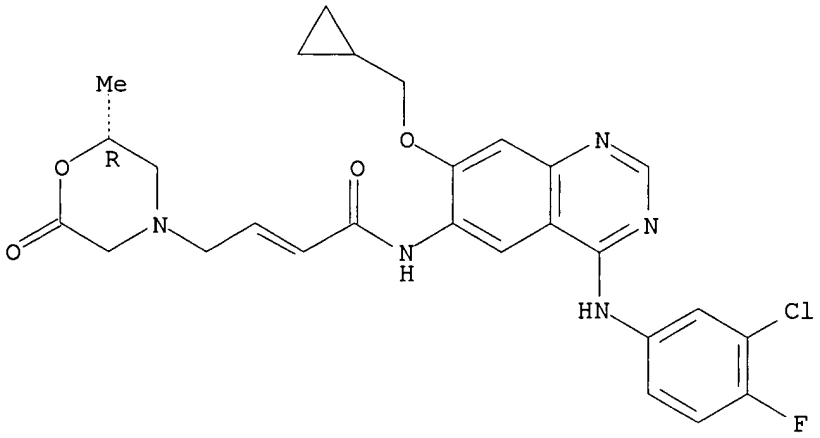
yl)amino]-7-cyclopropylmethoxyquinazoline. Several I inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.02-15 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

IT **402855-53-2P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402855-53-2 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



IT **402855-17-8P 402855-19-0P 402855-22-5P**
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402855-55-4P 402855-56-5P 402855-57-6P
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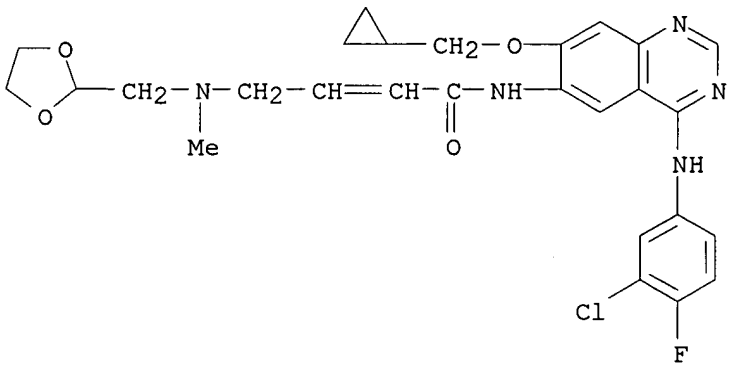
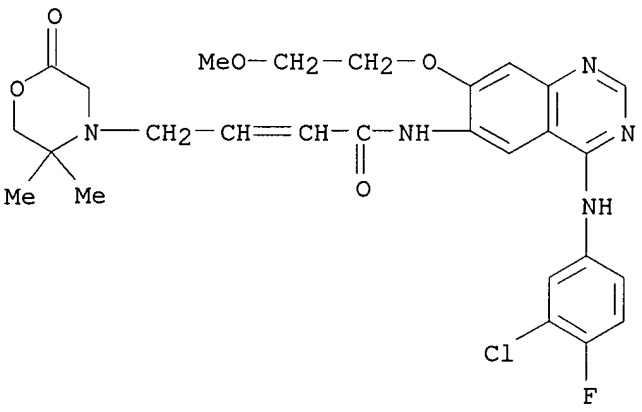
402855-61-2P 402855-62-3P 402855-64-5P
402855-66-7P 402855-67-8P 402855-69-0P
402855-70-3P 402855-71-4P 402855-72-5P
402855-73-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (amino)(vinylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402855-17-8 CAPLUS

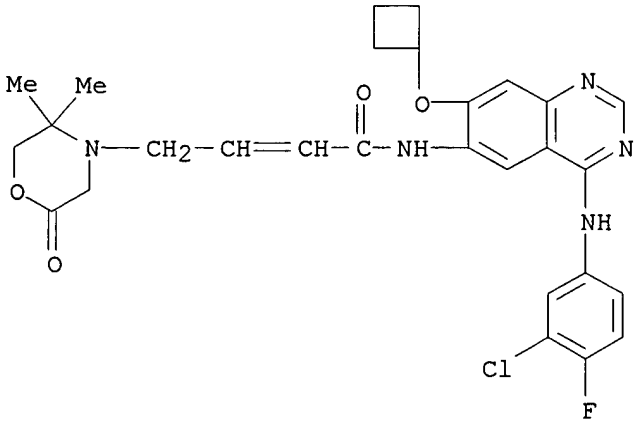
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(1,3-dioxolan-2-ylmethyl)methylamino]- (9CI) (CA INDEX NAME)



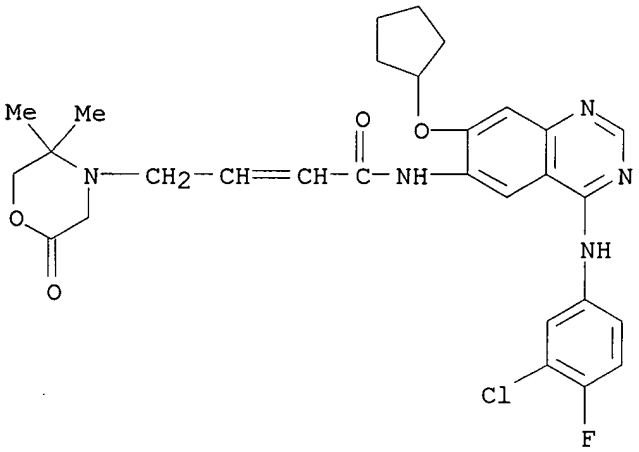
RN 402855-19-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(2-methoxyethoxy)-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)



RN 402855-22-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

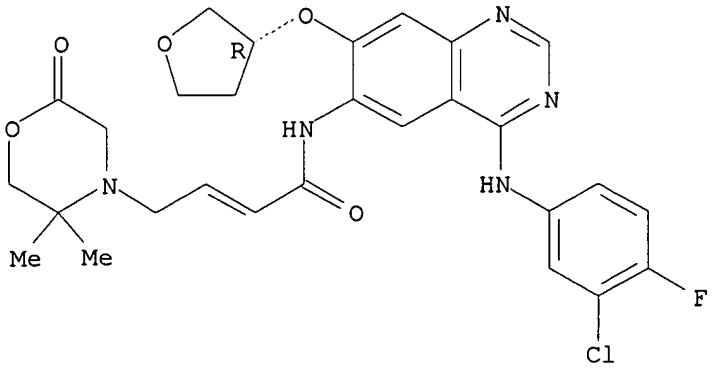


RN 402855-23-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)



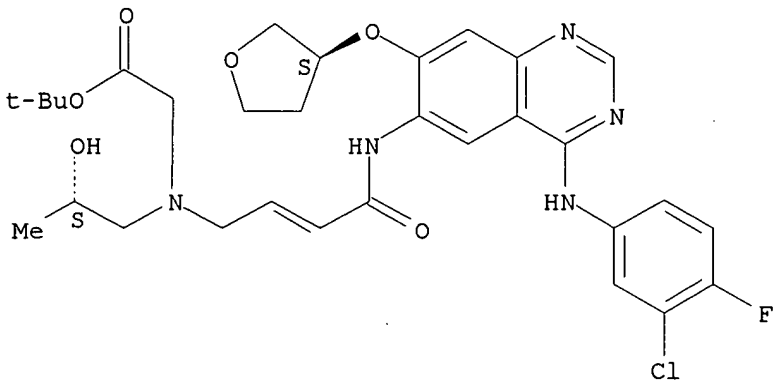
RN 402855-25-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3R)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



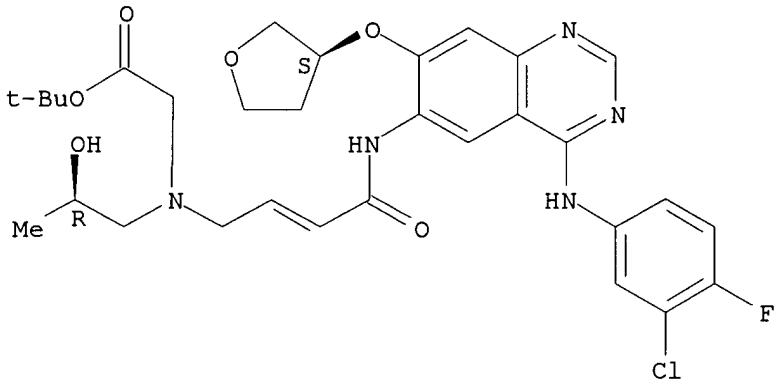
RN 402855-26-9 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2S)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



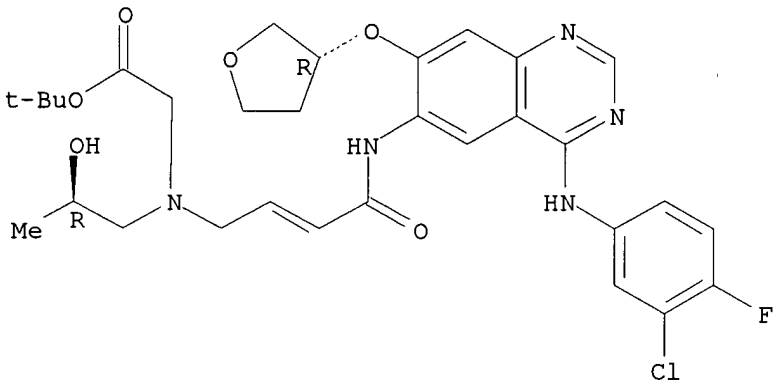
RN 402855-27-0 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

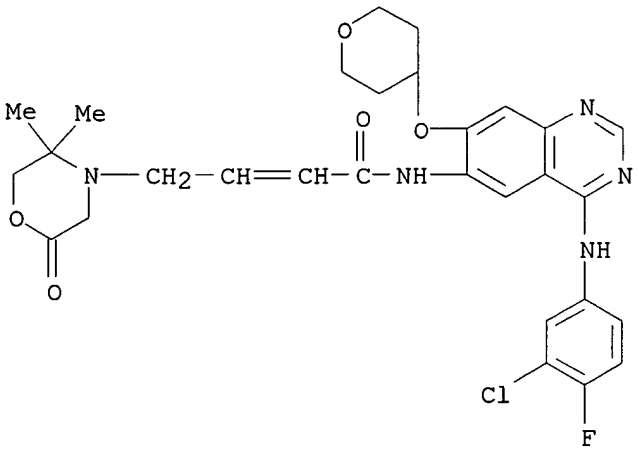


RN 402855-28-1 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3R)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

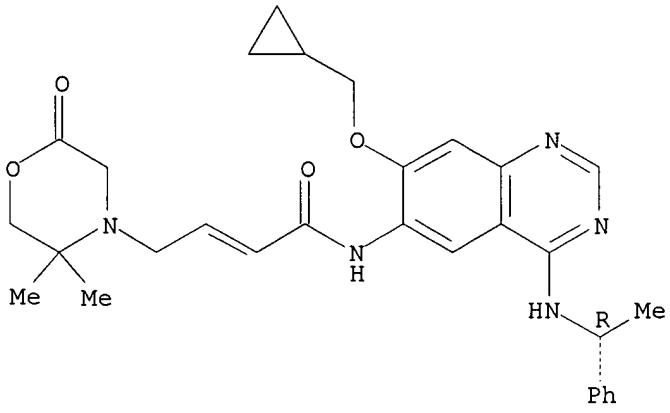


RN 402855-29-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)oxy]-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

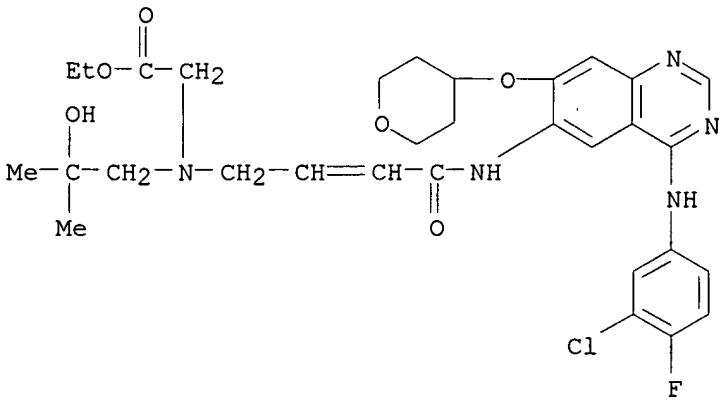


RN 402855-30-5 CAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

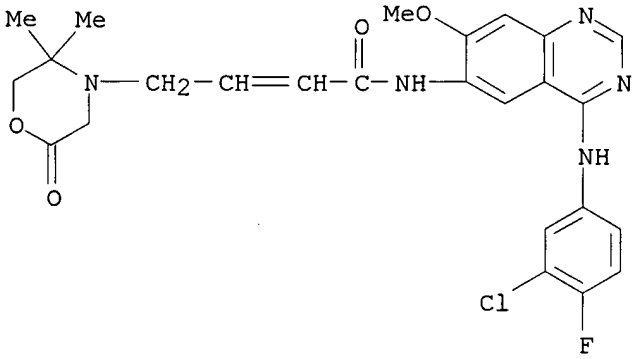
Absolute stereochemistry.
Double bond geometry unknown.



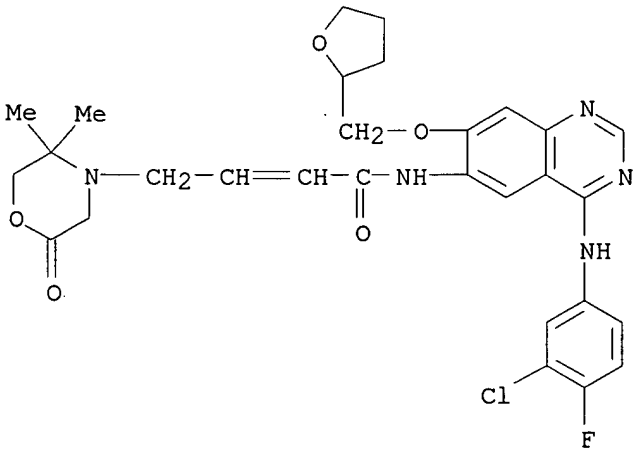
RN 402855-31-6 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)oxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-(2-hydroxy-2-methylpropyl)-, ethyl ester (9CI) (CA INDEX NAME)



RN 402855-32-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

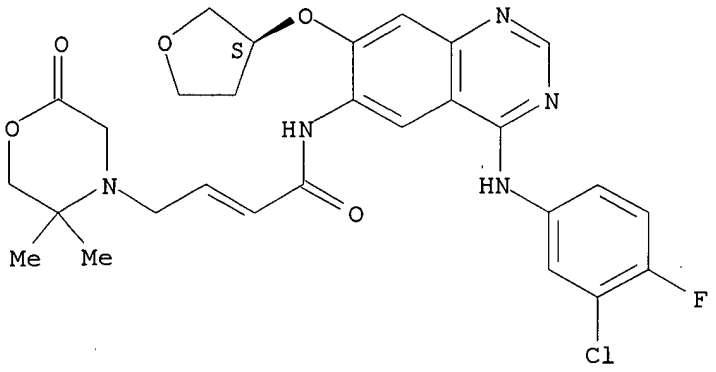


RN 402855-33-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2-furanyl)methoxy]-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

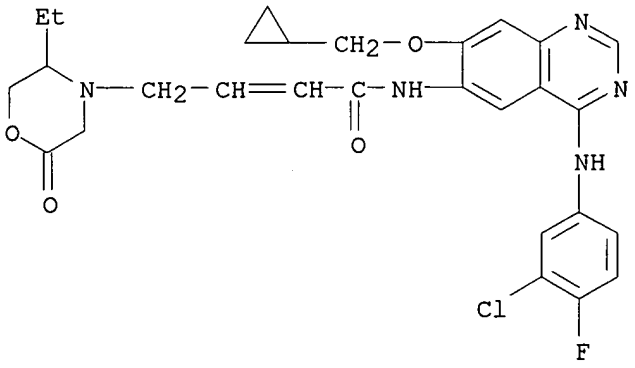


RN 402855-34-9 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

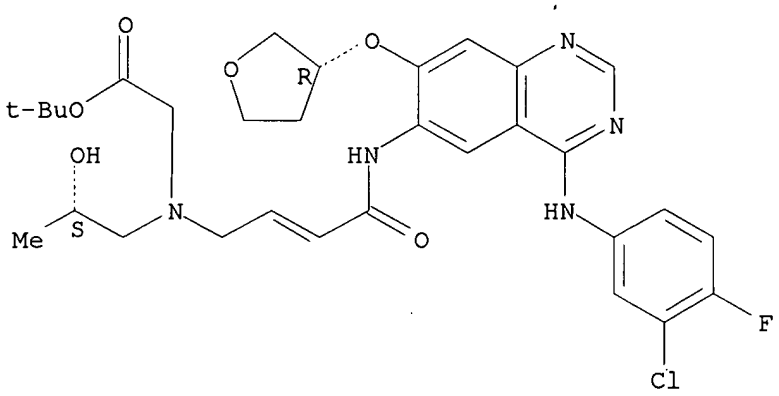


RN 402855-35-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(5-ethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)



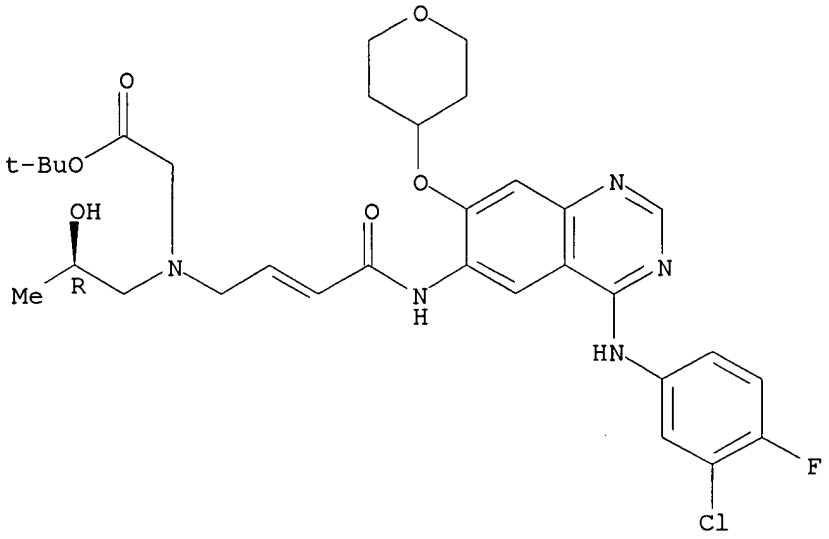
RN 402855-37-2 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3R)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2S)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



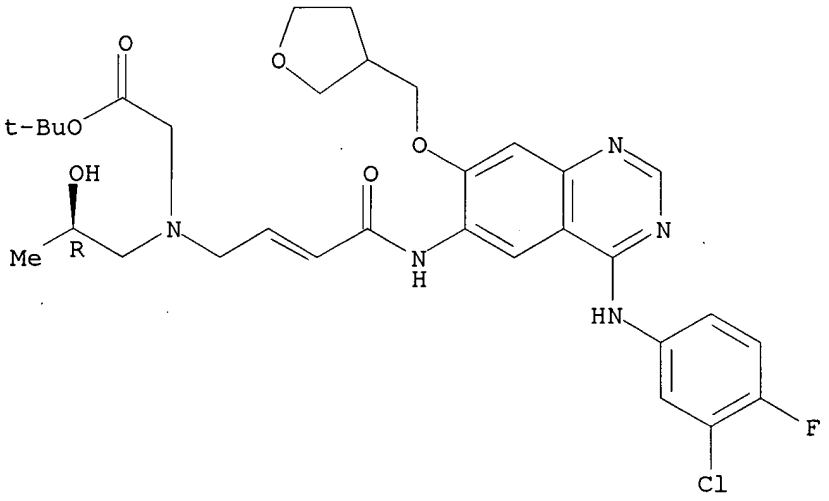
RN 402855-40-7 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)oxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

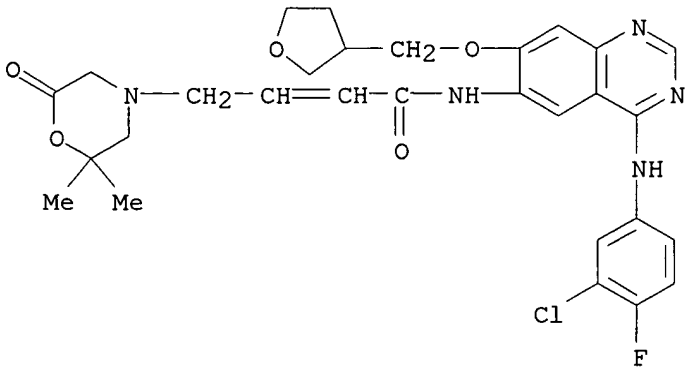


RN 402855-46-3 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-3-furanyl)methoxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

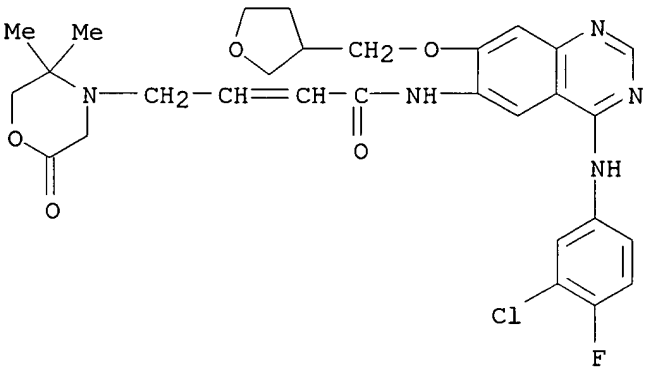
Absolute stereochemistry.
Double bond geometry unknown.



RN 402855-47-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-3-furanyl)methoxy]-6-quinazolinyl]-4-(2,2-dimethyl-6-oxo-4-morpholinyl)-(9CI) (CA INDEX NAME)

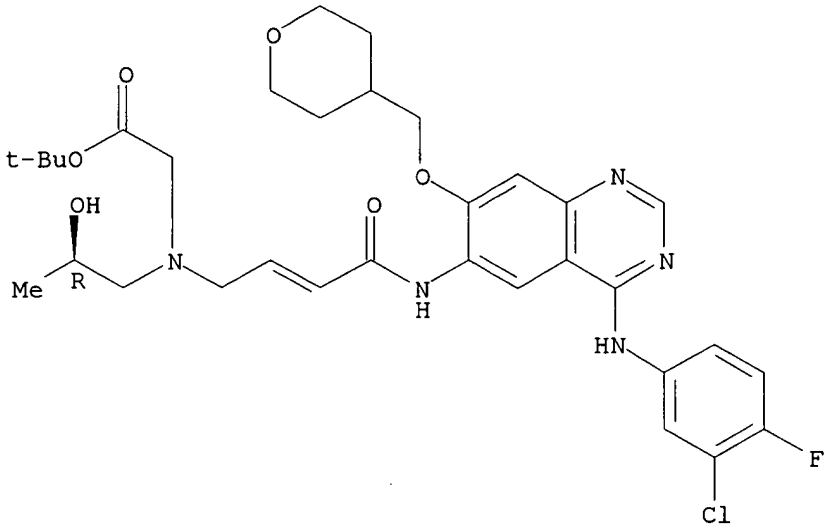


RN 402855-48-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-3-furanyl)methoxy]-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)-(9CI) (CA INDEX NAME)



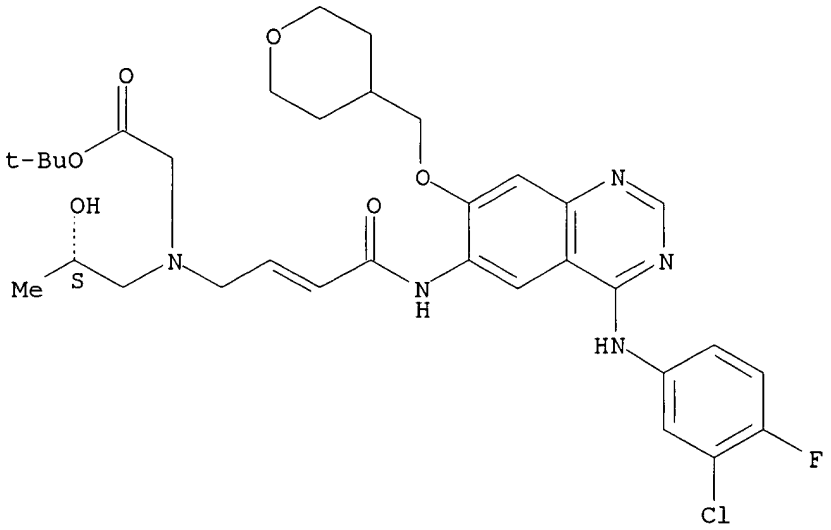
RN 402855-49-6 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)methoxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



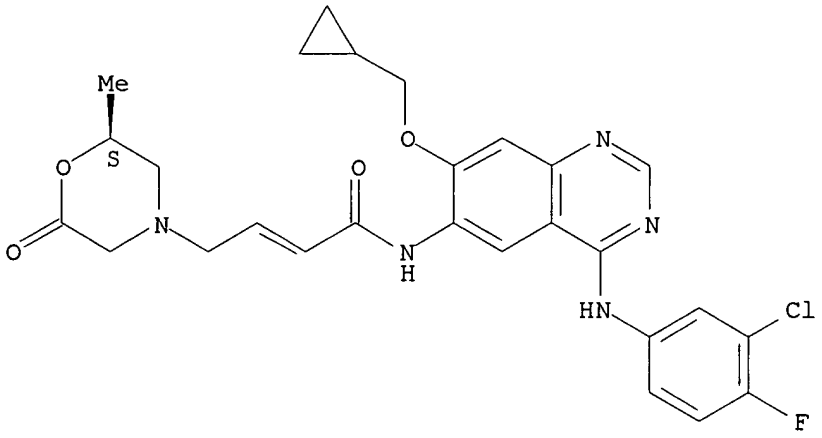
RN 402855-51-0 CAPLUS
CN Glycine, N-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)methoxy]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-N-[(2S)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



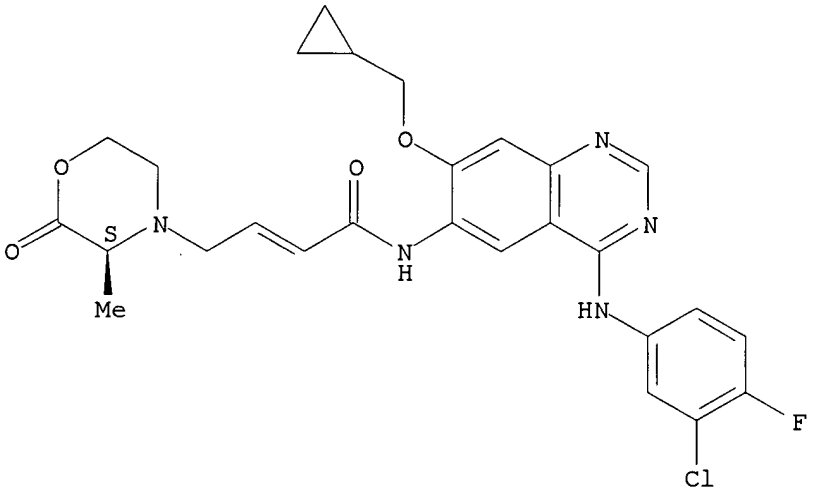
RN 402855-52-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



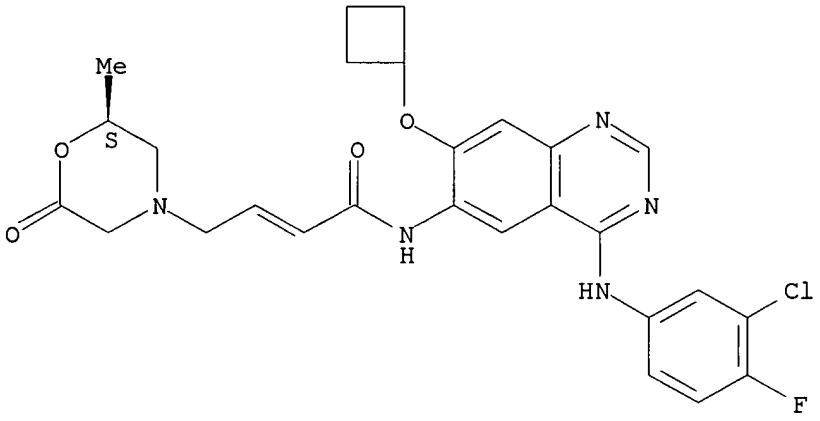
RN 402855-54-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(3S)-3-methyl-2-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



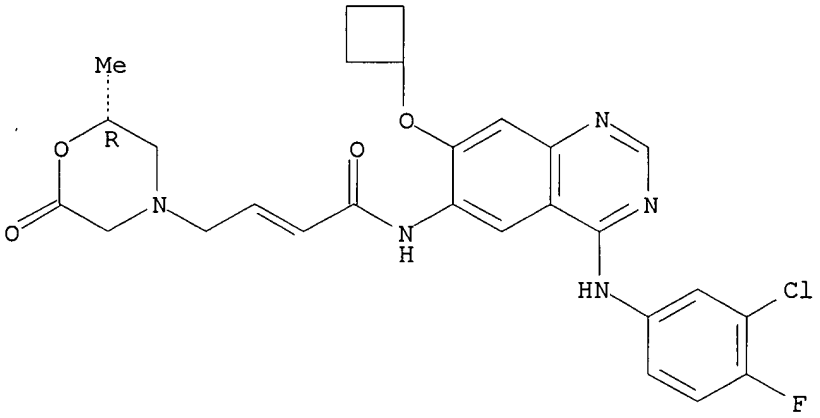
RN 402855-55-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



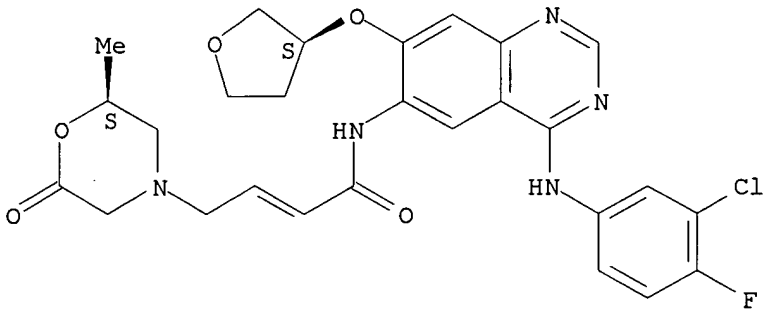
RN 402855-56-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



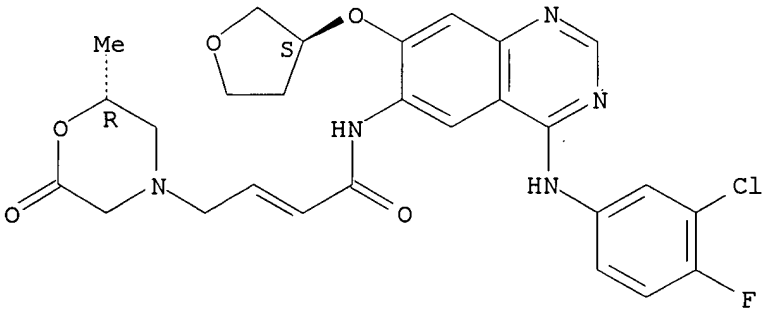
RN 402855-57-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



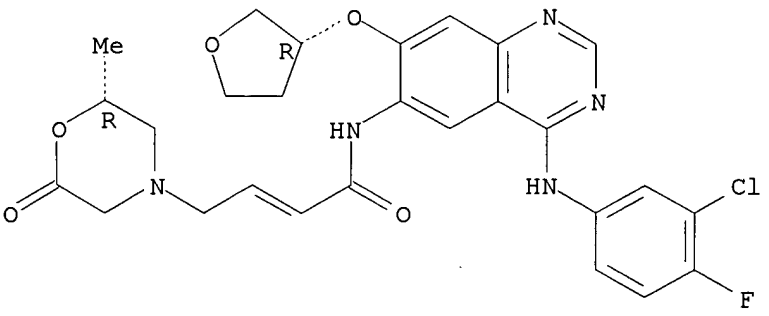
RN 402855-58-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



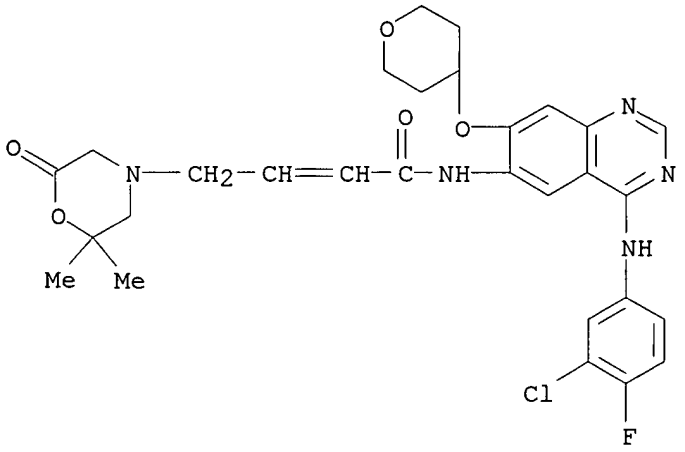
RN 402855-59-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3R)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



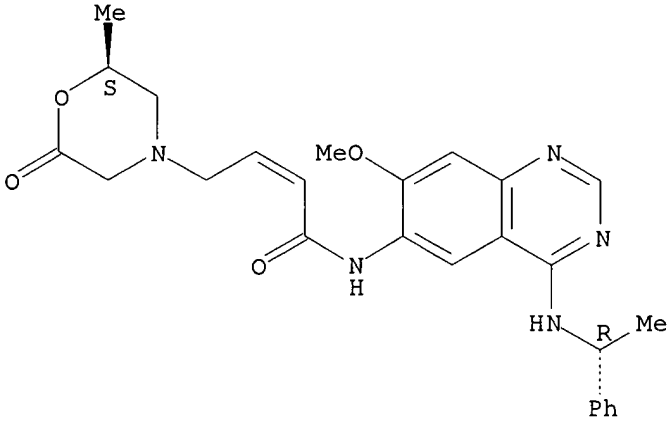
RN 402855-60-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-

pyran-4-yl)oxy]-6-quinazolinyl]-4-(2,2-dimethyl-6-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)



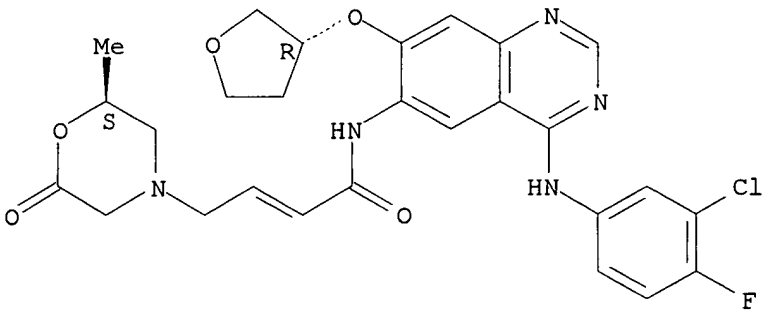
RN 402855-61-2 CAPLUS
CN 2-Butenamide, N-[7-methoxy-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



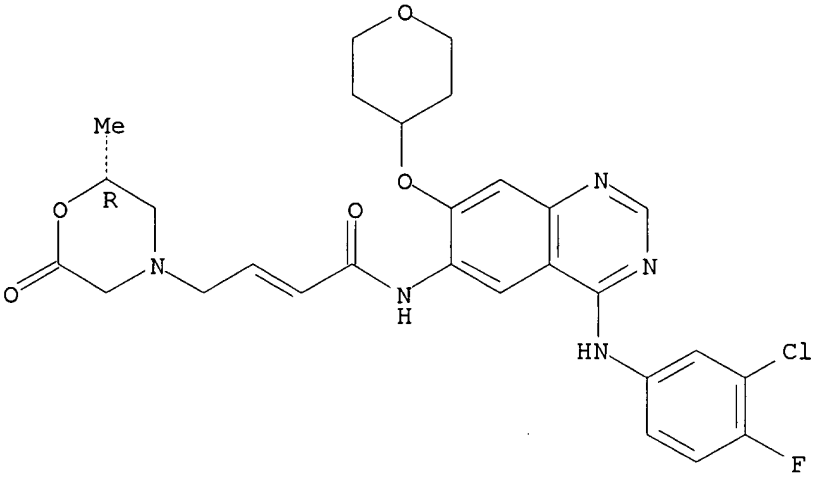
RN 402855-62-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3R)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



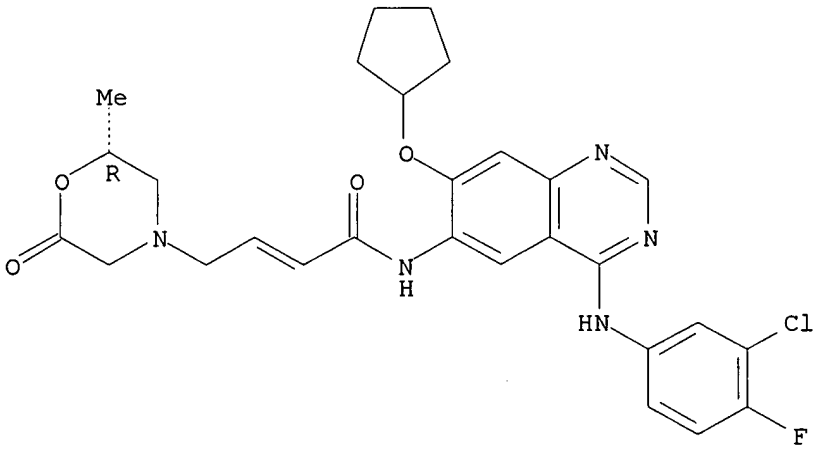
RN 402855-64-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)oxy]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



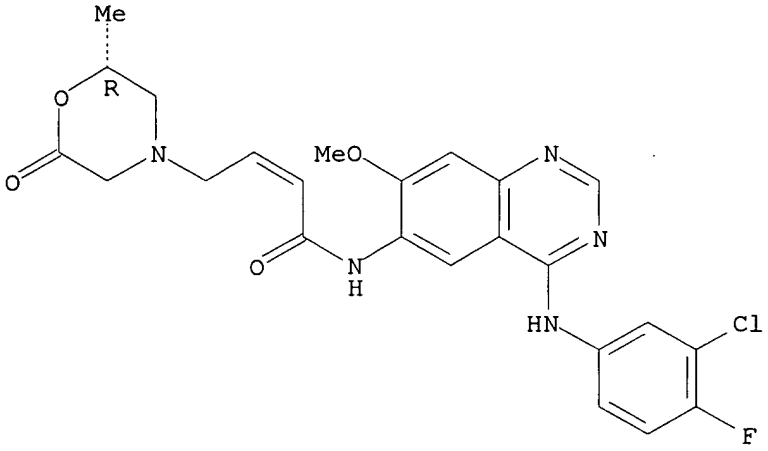
RN 402855-66-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



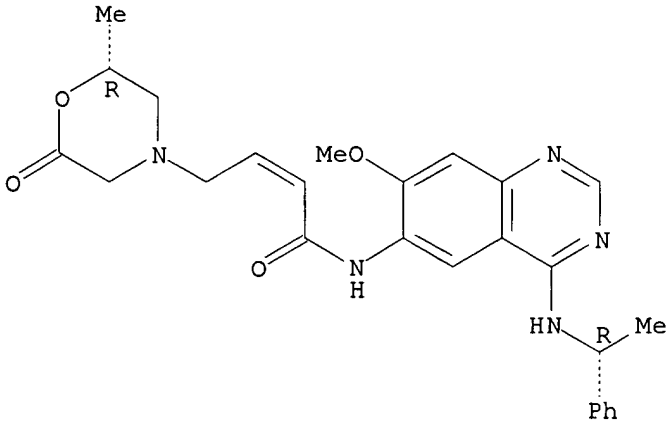
RN 402855-67-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



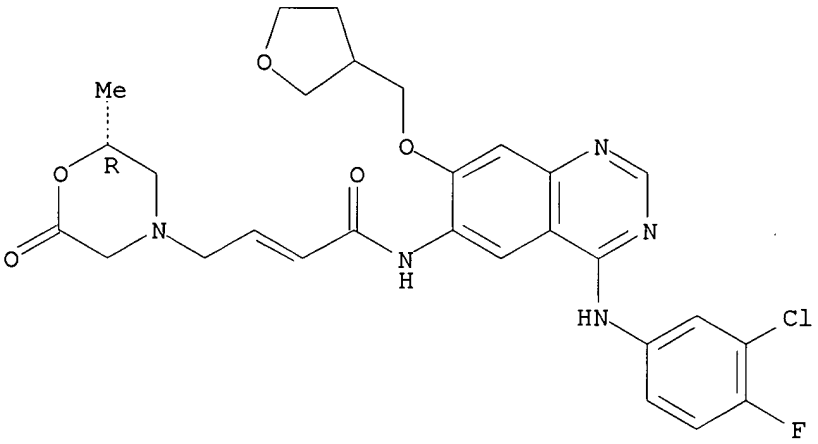
RN 402855-69-0 CAPLUS
CN 2-Butenamide, N-[7-methoxy-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



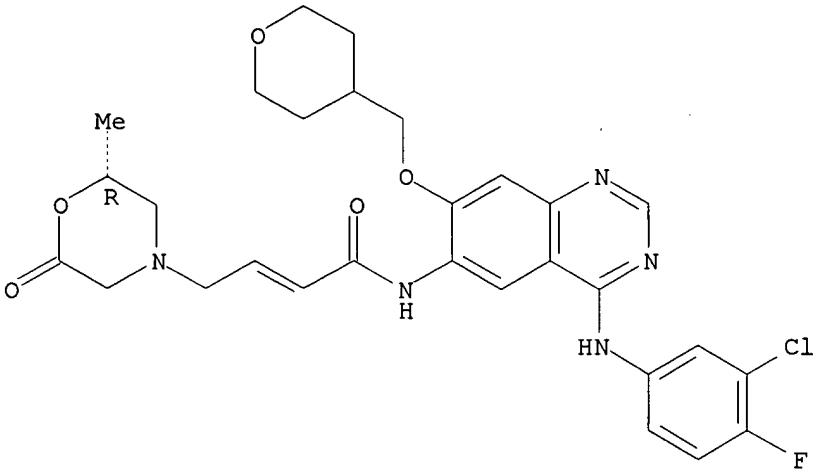
RN 402855-70-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-3-furanyl)methoxy]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



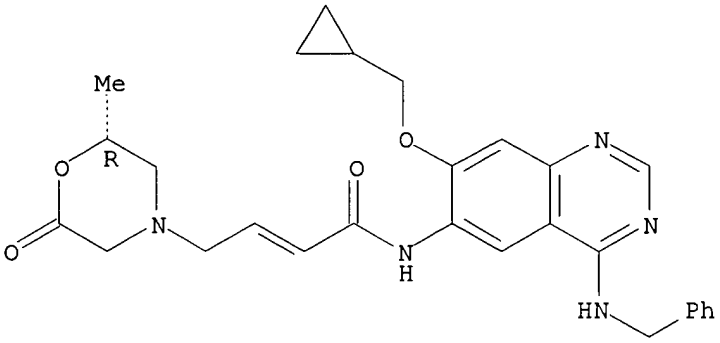
RN 402855-71-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)methoxy]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



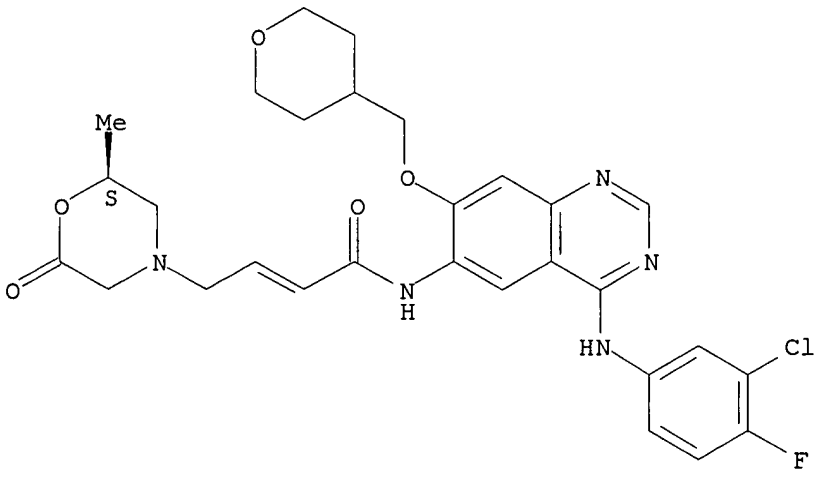
RN 402855-72-5 CAPLUS
CN 2-Butenamide, N-[7-(cyclopropylmethoxy)-4-[(phenylmethyl)amino]-6-quinazolinyl]-4-[(2R)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 402855-73-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)methoxy]-6-quinazolinyl]-4-[(2S)-2-methyl-6-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



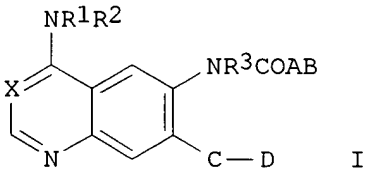
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

applicants

L17 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:171886 CAPLUS
DN 136:216758
TI Preparation of 4-amino-6-heterocyclylcarbonylaminoquinazolines as epidermal growth factor receptor signal transduction inhibitors
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma Kg, Germany
SO PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002018370	A1	20020307	WO 2001-EP9535	20010818
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	DE 10042061	A1	20020307	DE 2000-10042061	20000826
	AU 2001089814	A5	20020313	AU 2001-89814	20010818
	US 2002082270	A1	20020627	US 2001-934753	20010822
PRAI	DE 2000-10042061	A	20000826		
	US 2000-230119P	P	20000905		
	WO 2001-EP9535	W	20010818		

OS MARPAT 136:216758
GI



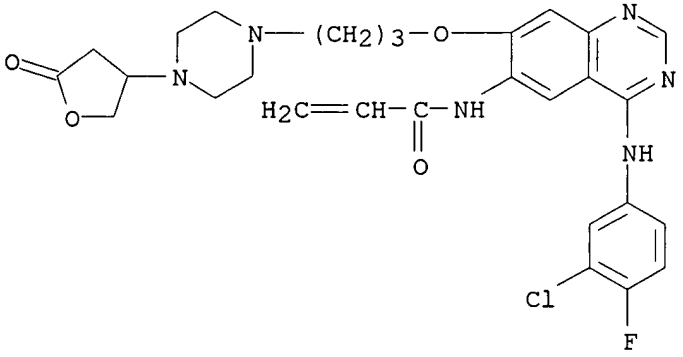
I

AB Title compds. [I; X = N, (substituted) methynyl; R1 = H, Me; R2 = (substituted) Ph, PhCH2, 1-phenylethyl; R3 = H, Me; A = (substituted) vinyl, ethynyl, 1,3-butadien-1,4-yl; B = H, (substituted) alkyl, alkylcarbonyl, CO2H, alkoxycarbonyl, aminocarbonyl, (di)alkylaminocarbonyl, pyrrolidinylcarbonyl, piperidinylcarbonyl, morpholinocarbonyl, alkylpiperazinylcarbonyl; C = (oxy)alkenyl, O; D = (substituted) pyrrolidinyl, piperidinyl, hexahydroazepinyl, piperazinyl, etc.], were prepd. Thus, a mixt. of CH2:CHCO2H and Et3N was stirred for 45 min at -50.degree. with CH2:CHCO2Cl in THF followed by dropwise addn. of 6-amino-4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propyloxy)quinazoline (prepn. given) in THF for 20 min and stirring at 0.degree. up to completely conversion to give 31% 4-[(3-chloro-4-fluorophenyl)amino]-7-(3-[4-(2-oxotetrahydrofuran-4-yl)piperazin-1-yl]propyloxy)-6-

[(vinylcarbonyl)amino]quinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 12 nM. The invention relates to the use of the title compds. for treating tumor diseases, and lung and respiratory tract disorders.

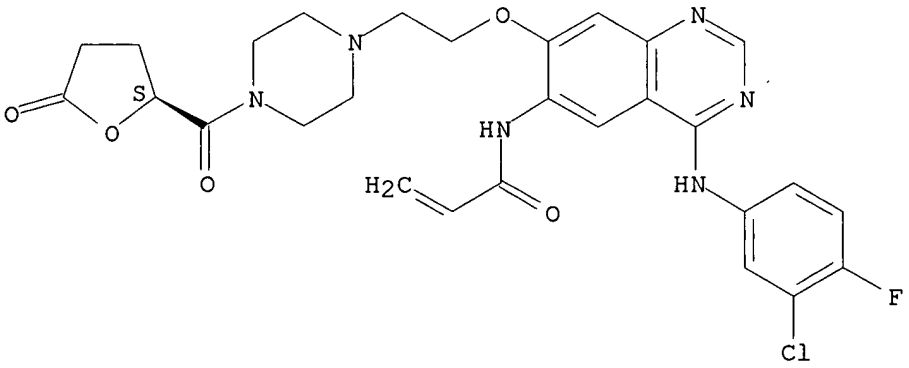
IT **402496-84-8P 402496-85-9P 402496-86-0P 402496-87-1P 402496-88-2P 402496-89-3P 402496-90-6P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of (amino)(heterocyclylcarbonylamino)quinazolines as epidermal growth factor receptor signal transduction inhibitors)

RN 402496-84-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



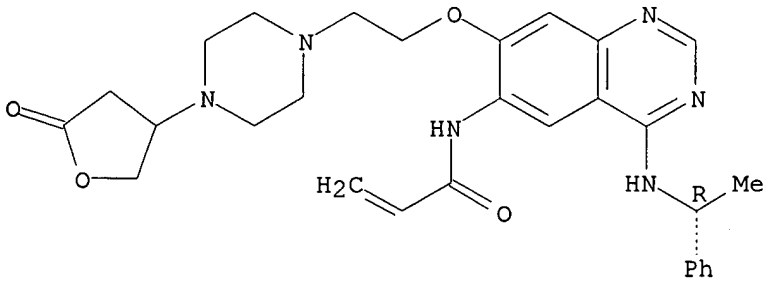
RN 402496-85-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-[4-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-1-piperazinyl]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

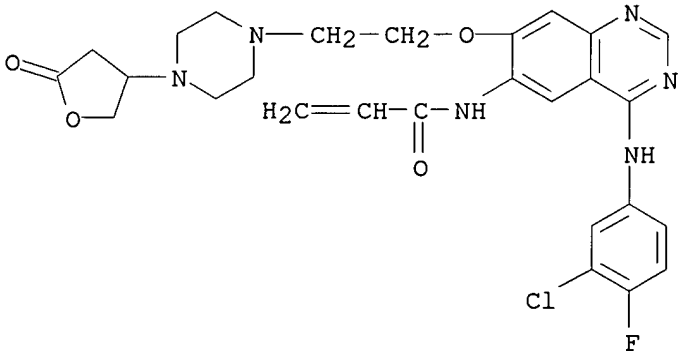


RN 402496-86-0 CAPLUS
CN 2-Propenamide, N-[4-[[(1R)-1-phenylethyl]amino]-7-[2-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

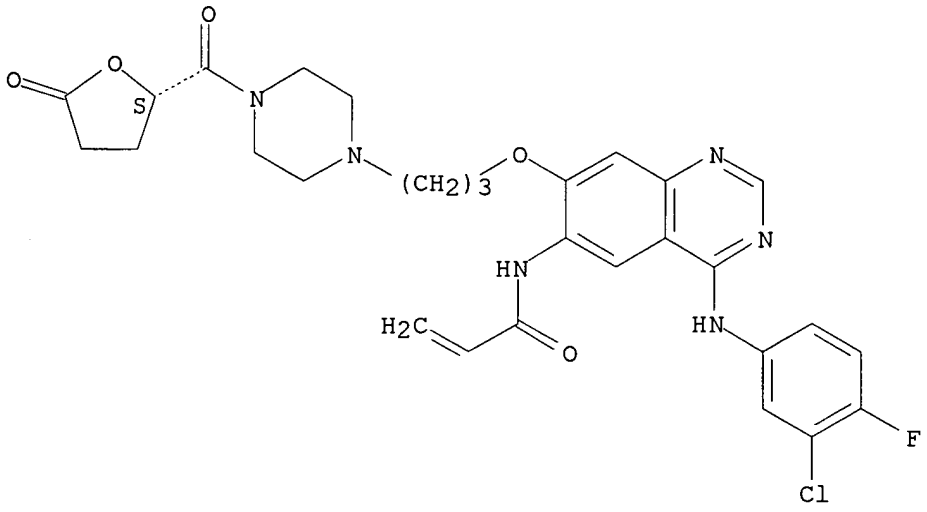


RN 402496-87-1 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[2-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

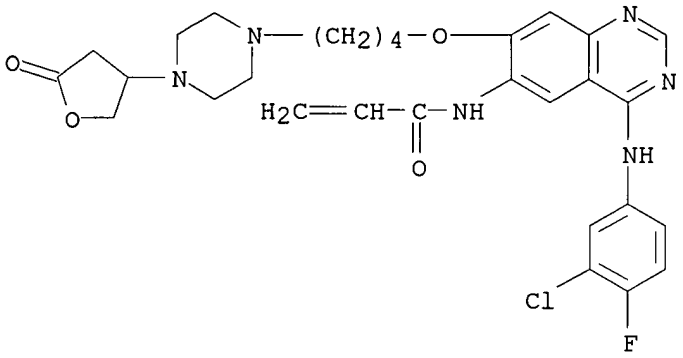


RN 402496-88-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-[4-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-1-piperazinyl]propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

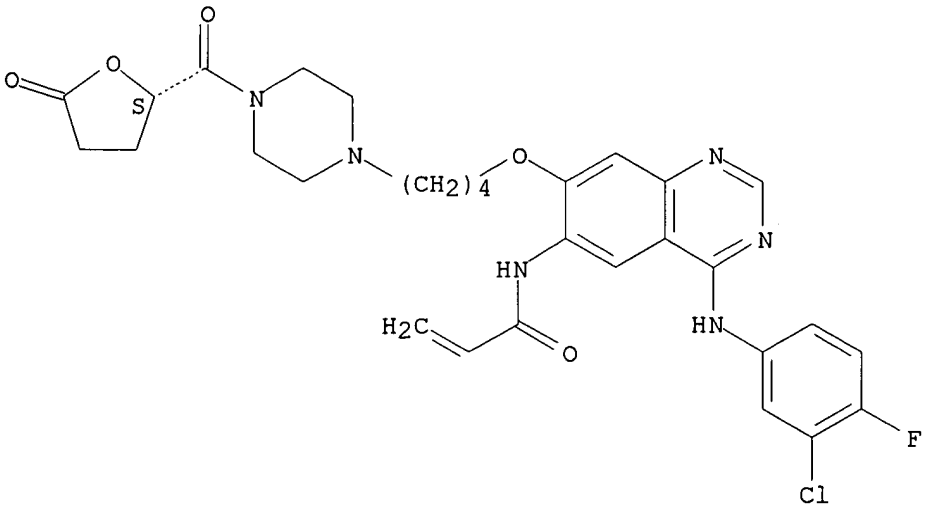


RN 402496-89-3 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 402496-90-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[4-[4-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-1-piperazinyl]butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

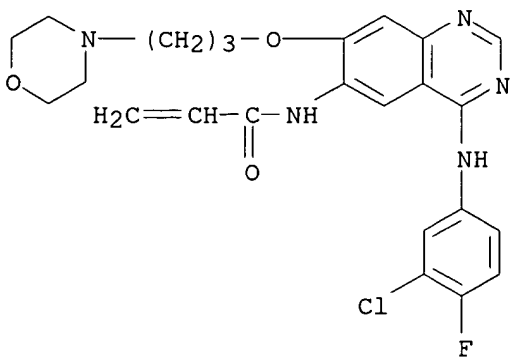
L17 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2002:10449 CAPLUS
DN 136:74658
TI Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)-quinazolin-6-yl]acrylamide dihydrochloride
IN Barth, Hubert; Steiner, Klaus; Schneider, Simon; Huels, Dietmar; Muehlenfeld, Andreas; Westermayer, Manfred
PA Goedecke G.m.b.H., Germany
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002000630	A1	20020103	WO 2001-EP6733	20010615
	W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CO, CR, CU, CZ, DM, DZ, EC, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	DE 10031971	A1	20020110	DE 2000-10031971	20000630
	EP 1299363	A1	20030409	EP 2001-962739	20010615
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	NO 2002006193	A	20030127	NO 2002-6193	20021223
PRAI	DE 2000-10031971	A	20000630		
	WO 2001-EP6733	W	20010615		

AB Polymorphic forms/hydrates of N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quinazolin-6-yl]acrylamide-2HCl (I), processes for their prepn., as well as their use for the prepn. of pharmaceuticals with irreversible tyrosine kinase inhibiting action are described. N-[4-(3-chloro-4-fluorophenylamino)-7-(3-morpholin-4-ylpropoxy)quinazolin-6-yl]acrylamide was dissolved in EtOH and treated with HCl to give I monohydrate (Form M). The compd. was thermally stable when subjected to different thermal stress conditions.

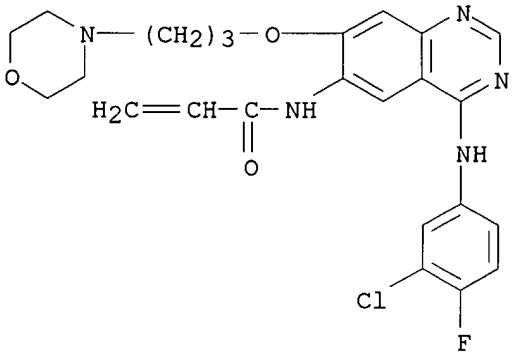
IT **289499-45-2P 383908-86-9P 383908-87-0P 383908-88-1P**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polymorphic forms/hydrates of (chlorofluorophenylamino)morpholinylpropoxyquinazolinylacrylamide)

RN 289499-45-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride (9CI) (CA INDEX NAME)



● 2 HCl

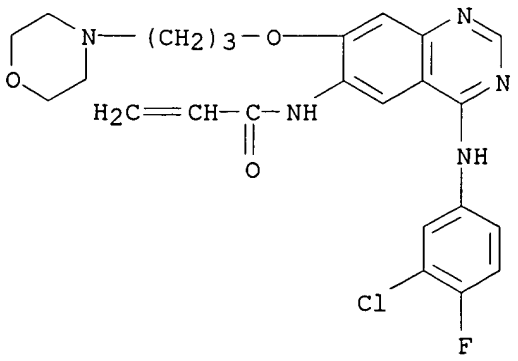
RN 383908-86-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, monohydrate (9CI) (CA INDEX NAME)



● 2 HCl

● H_2O

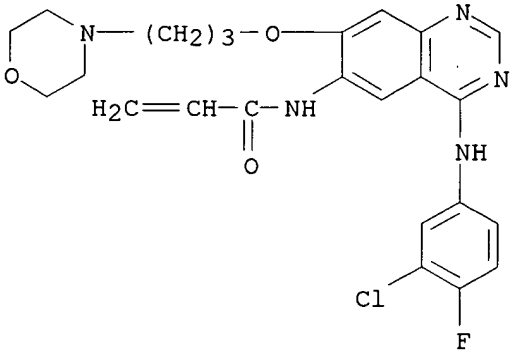
RN 383908-87-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, trihydrate (9CI) (CA INDEX NAME)



●2 HCl

●3 H_2O

RN 383908-88-1 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, heptahydrate (9CI) (CA INDEX NAME)

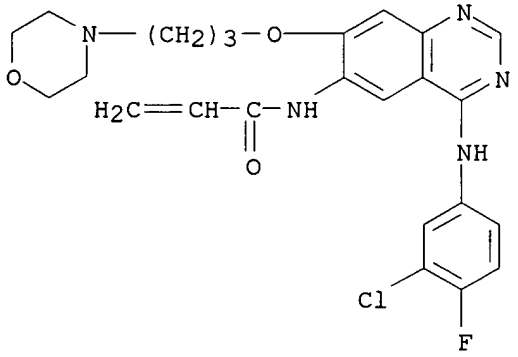


●2 HCl

●7 H_2O

IT **267243-28-7**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(prepn. of polymorphic forms/hydrates of (chlorofluorophenylamino)morpholinylpropoxyquinazolinylacrylamide)

RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

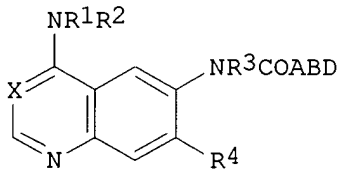


RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2001:762992 CAPLUS
DN 135:303907
TI Preparation of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction.
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma K.-G., Germany
SO PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10017539	A1	20011011	DE 2000-10017539	20000408
DE 10040525	A1	20020228	DE 2000-10040525	20000818
EP 1280798	A1	20030205	EP 2001-938076	20010331
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI DE 2000-10017539	A	20000408		
DE 2000-10040525	A	20000818		
WO 2001-EP3694	W	20010331		

OS MARPAT 135:303907
GI



I

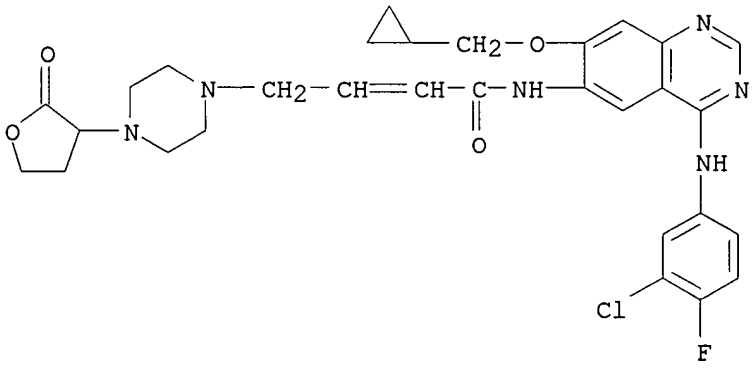
AB Title compds. [I; X = NCN, N; R1 = H, alkyl; R2 = (substituted) Ph, PhCH2, PhCH2CH2; R3 = H, alkyl; R4 = H, alkoxy, cycloalkoxy, cycloalkylalkoxy; A = (substituted) vinylene; B = bond, (fluoro)alkylene; D = substituted pyrrolidinyl, piperidinyl, piperazinyl, etc.], were prepd. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(piperazin-1-yl)-1-oxo-2-buten-1-yl]amino]-7-cyclopropylmethoxyquinazoline (prepn. given) in THF was treated with Et3N and then with 3-bromodihydrofuran-2-one in THF under ice cooling followed by stirring for 48 h at room temp. to give 56% 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-[4-(2-oxotetrahydrofuran-3-yl)piperazin-1-yl]-1-oxo-2-buten-1-yl]amino]-7-

cyclopropylmethoxyquinazoline. The latter inhibited epidermal growth factor (EGF)-dependent proliferation of F/L-HERc cells with IC50 = 0.05 nM.

IT **365532-35-0P 365532-36-1P 365532-37-2P**
365532-39-4P 365532-40-7P 365532-41-8P
365532-42-9P 365532-44-1P 365532-45-2P
365532-46-3P 365532-47-4P 365532-48-5P
365532-49-6P 367282-07-3P 367282-12-0P
367282-15-3P 367282-23-3P 367282-25-5P
367282-27-7P 367282-29-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)

RN 365532-35-0 CAPLUS

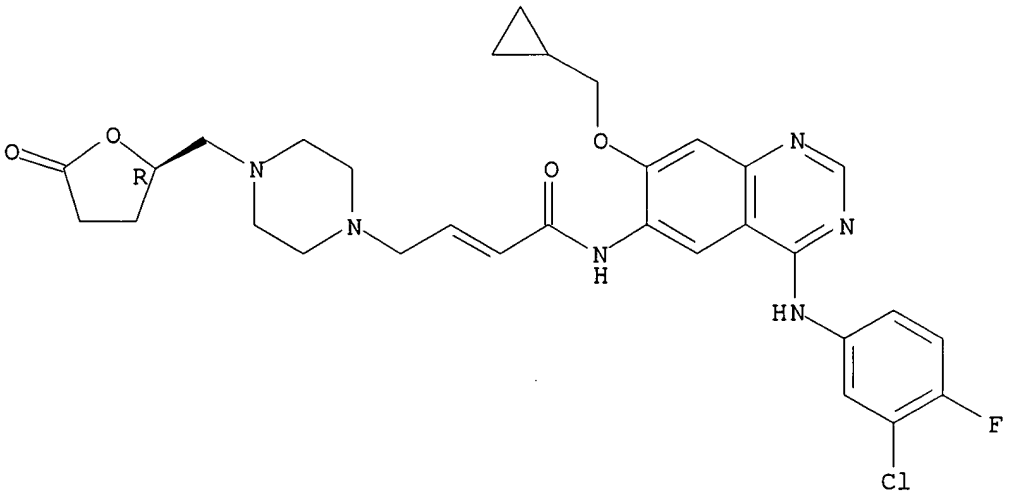
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)



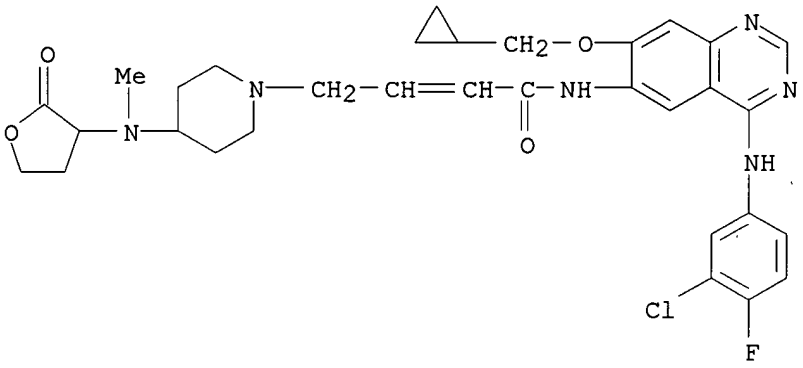
RN 365532-36-1 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2R)-tetrahydro-5-oxo-2-furanyl]methyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

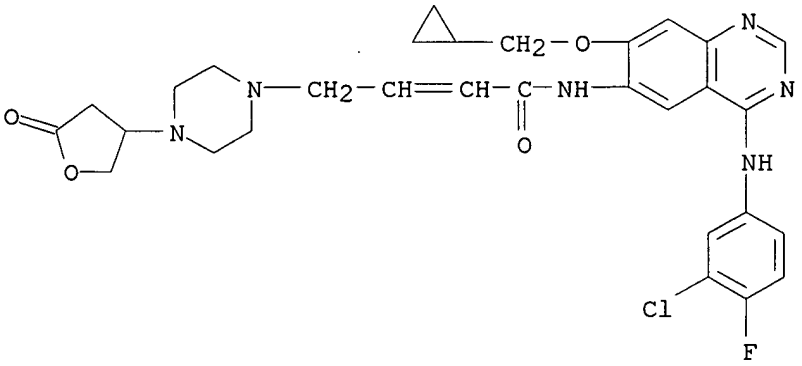
Absolute stereochemistry.
Double bond geometry unknown.



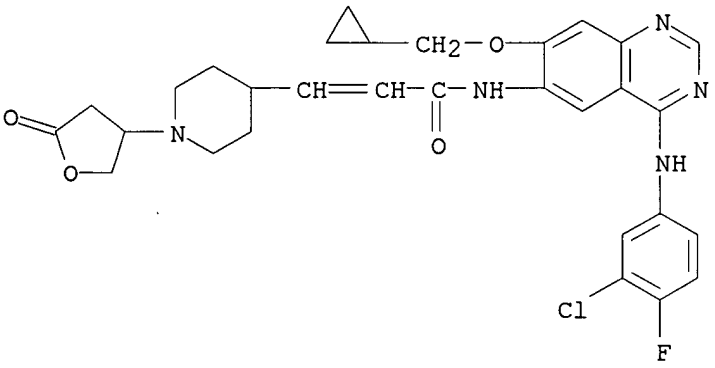
RN 365532-37-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[methyl(tetrahydro-2-oxo-3-furanyl)amino]-1-piperidinyl]- (9CI) (CA INDEX NAME)



RN 365532-39-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)

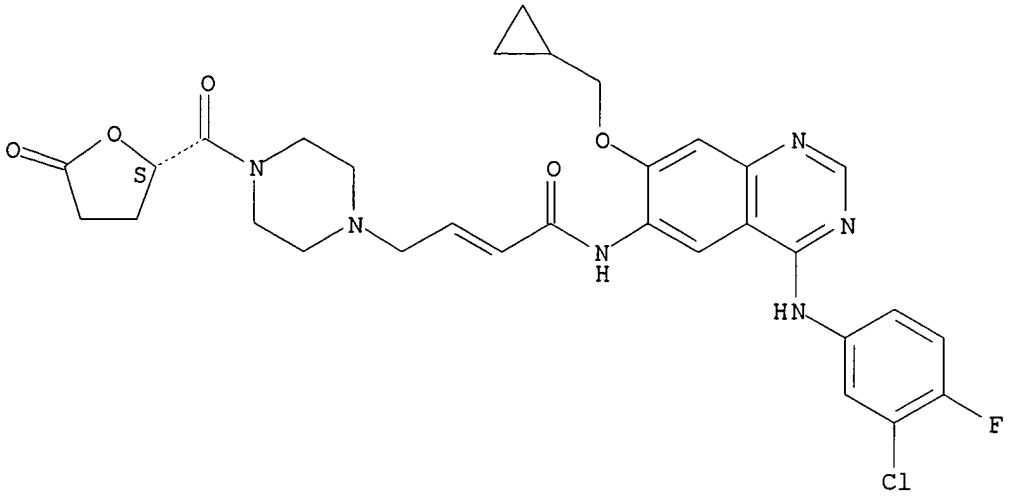


RN 365532-40-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-[1-(tetrahydro-5-oxo-3-furanyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)

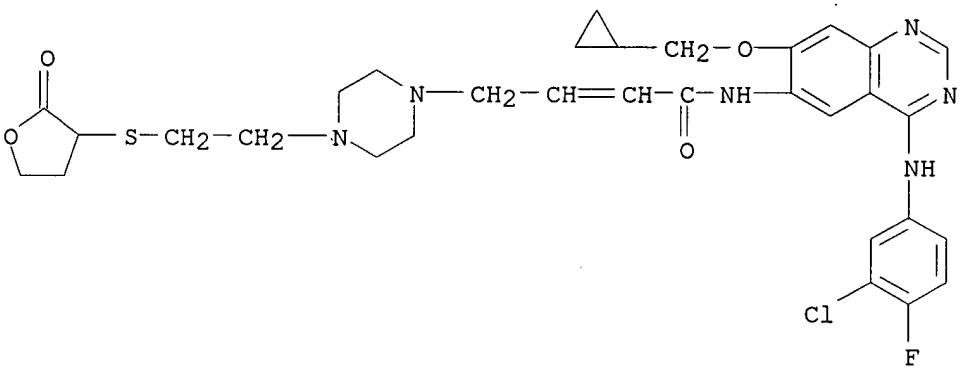


RN 365532-41-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

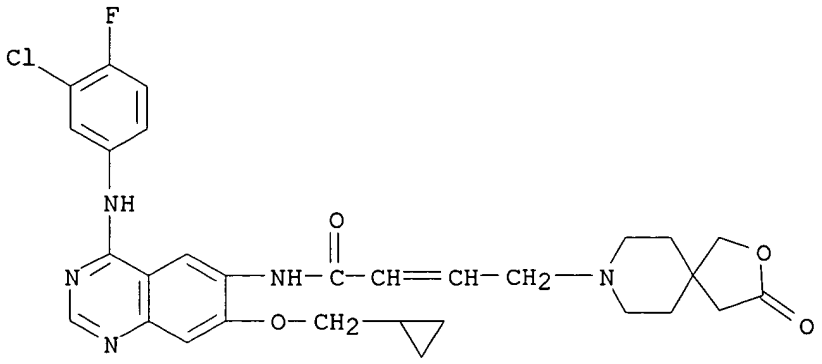
Absolute stereochemistry.
Double bond geometry unknown.



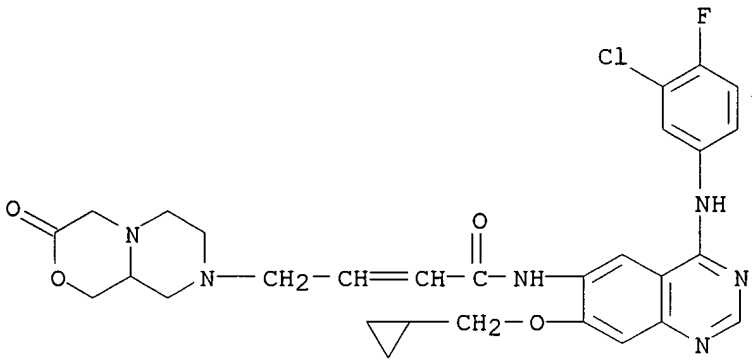
RN 365532-42-9 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[2-[(tetrahydro-2-oxo-3-furanyl)thio]ethyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)



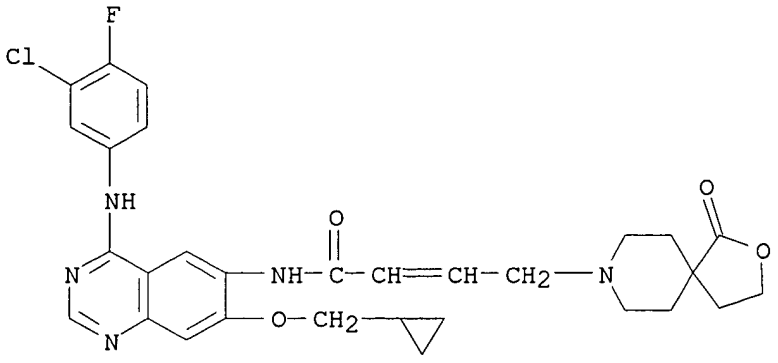
RN 365532-44-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(3-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)



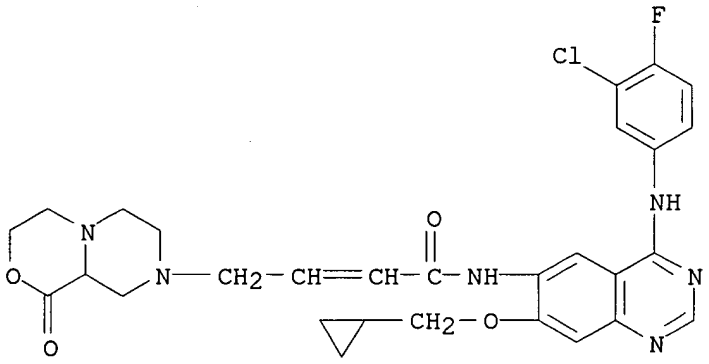
RN 365532-45-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-3-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)- (9CI) (CA INDEX NAME)



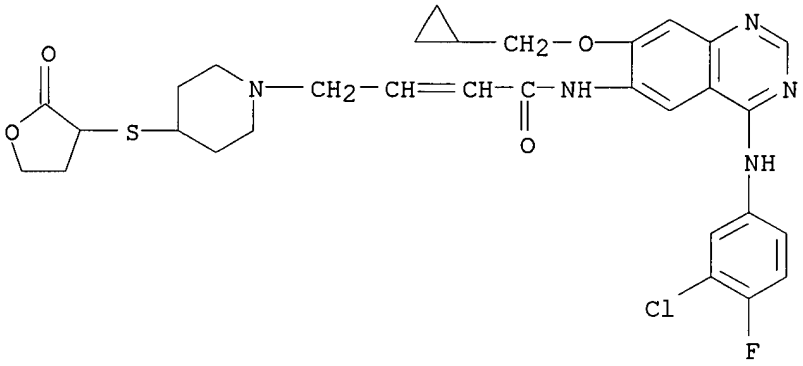
RN 365532-46-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)



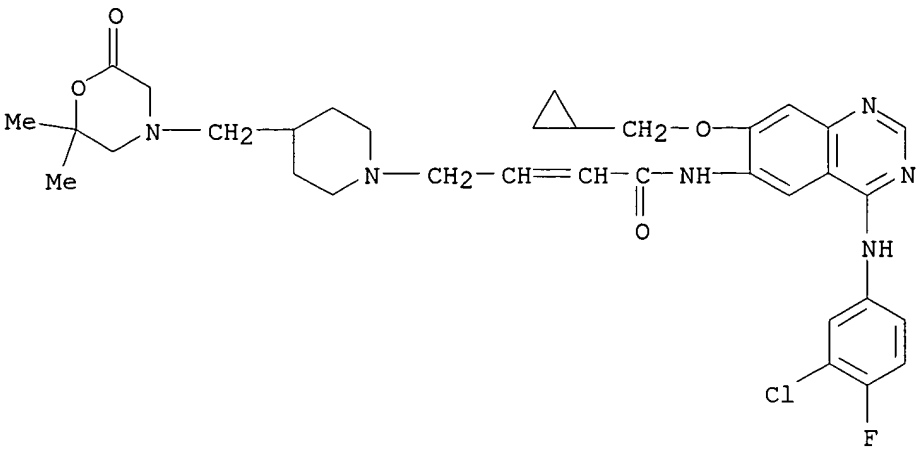
RN 365532-47-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-1-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)- (9CI) (CA INDEX NAME)



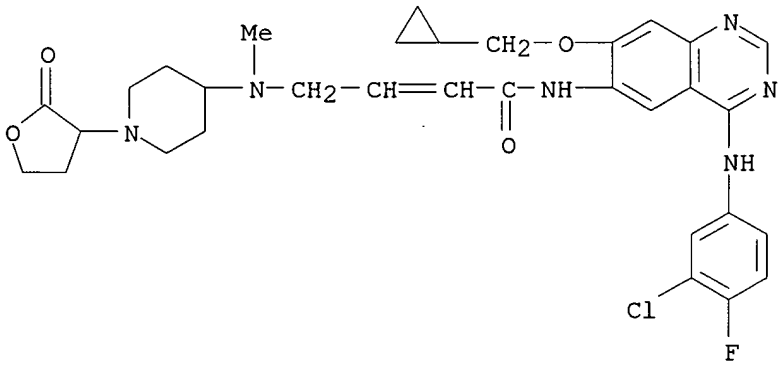
RN 365532-48-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(tetrahydro-2-oxo-3-furanyl)thio]-1-piperidinyl]- (9CI) (CA INDEX NAME)



RN 365532-49-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(2,2-dimethyl-6-oxo-4-morpholinyl)methyl]-1-piperidinyl]- (9CI) (CA INDEX NAME)



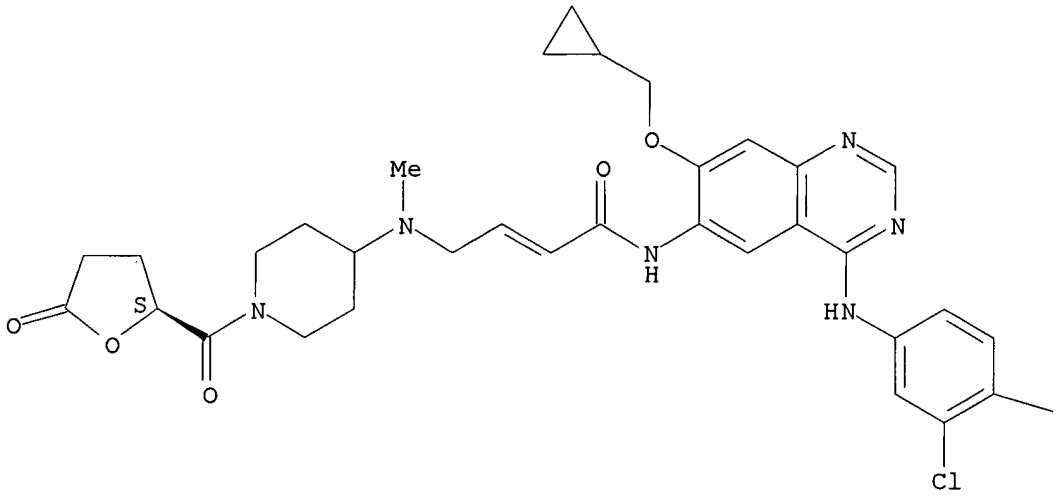
RN 367282-07-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[1-(tetrahydro-2-oxo-3-furanyl)-4-piperidinyl]amino]- (9CI) (CA INDEX NAME)



RN 367282-12-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[1-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-4-piperidinyl]amino]- (9CI) (CA INDEX NAME)

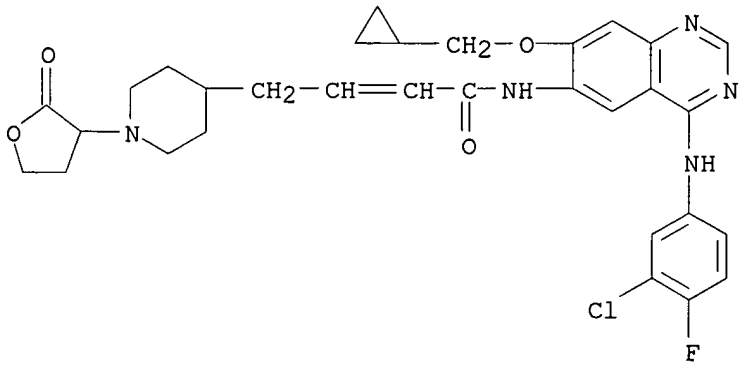
Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A

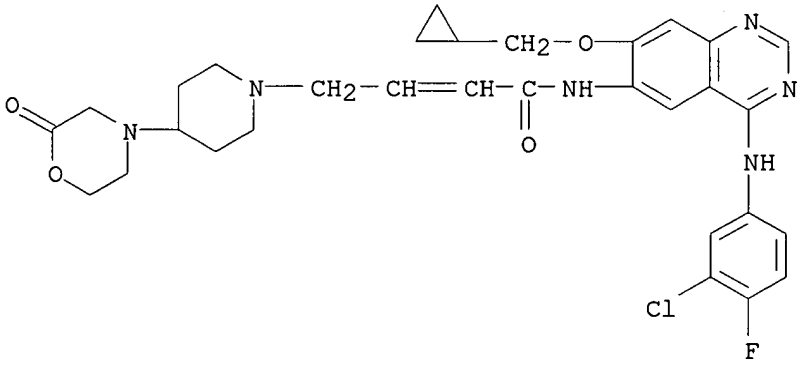


PAGE 1-B

RN 367282-15-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[1-(tetrahydro-2-oxo-3-furanyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)

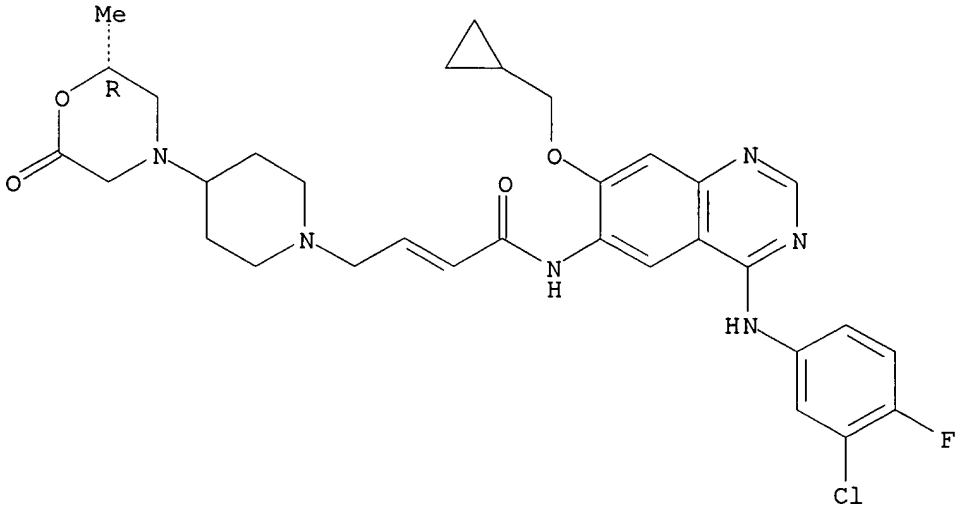


RN 367282-23-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(2-oxo-4-morpholinyl)-1-piperidinyl]- (9CI) (CA INDEX NAME)

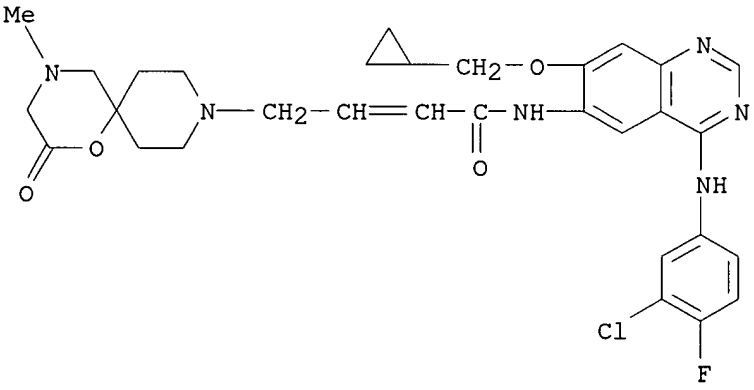


RN 367282-25-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(2R)-2-methyl-6-oxo-4-morpholinyl]-1-piperidinyl]- (9CI) (CA INDEX NAME)

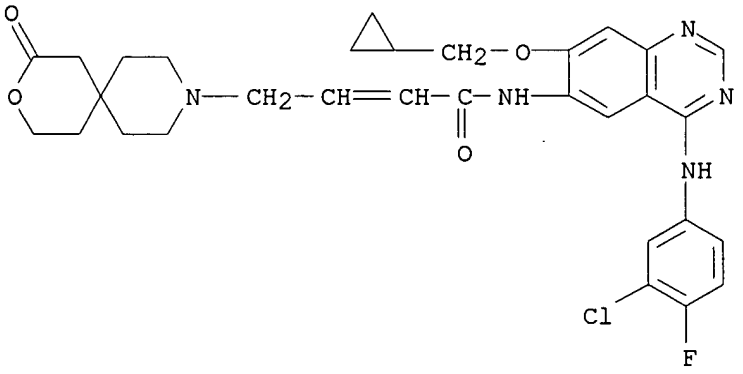
Absolute stereochemistry.
Double bond geometry unknown.



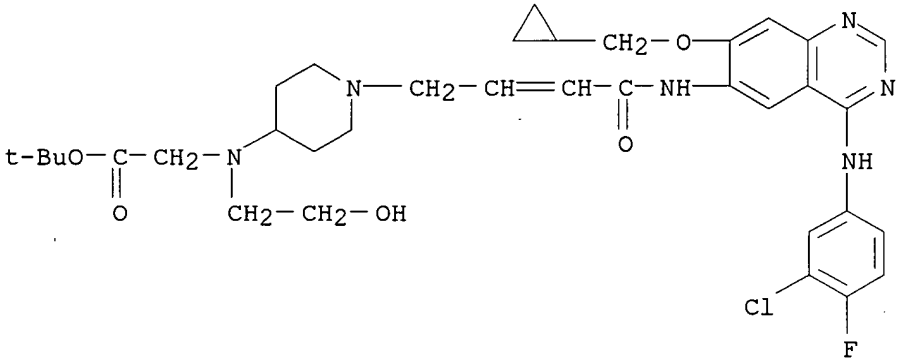
RN 367282-27-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-methyl-2-oxo-1-oxa-4,9-diazaspiro[5.5]undec-9-yl)- (9CI) (CA INDEX NAME)



RN 367282-29-9 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2-oxo-3-oxa-9-azaspiro[5.5]undec-9-yl)- (9CI) (CA INDEX NAME)

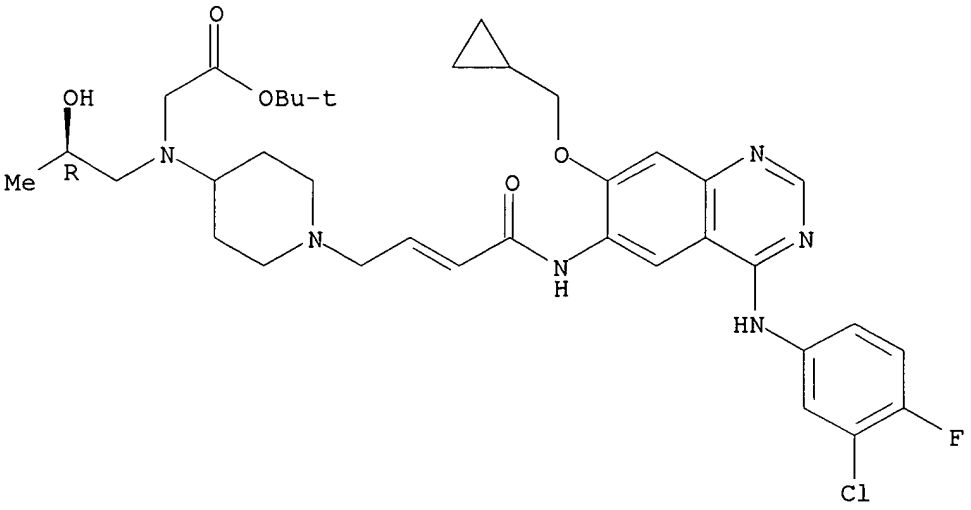


IT **367283-05-4 367283-07-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)
RN 367283-05-4 CAPLUS
CN Glycine, N-[1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]-N-(2-hydroxyethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 367283-07-6 CAPLUS
CN Glycine, N-[1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]-N-[(2R)-2-hydroxypropyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

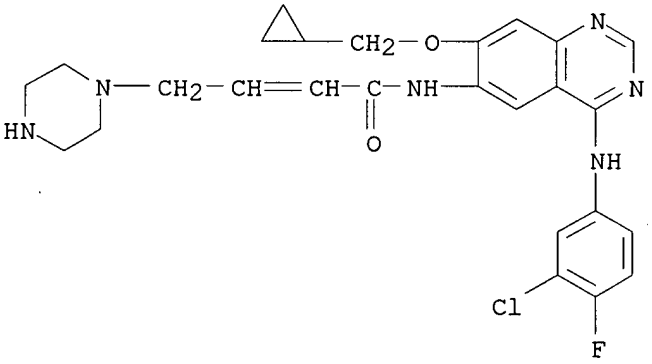
Absolute stereochemistry.
Double bond geometry unknown.



IT **290303-47-8P 290304-01-7P 365532-06-5P**
365532-07-6P 365532-18-9P 365532-19-0P
367282-36-8P 367282-44-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of quinazolines as inhibitors of epidermal growth factor-mediated signal transduction)

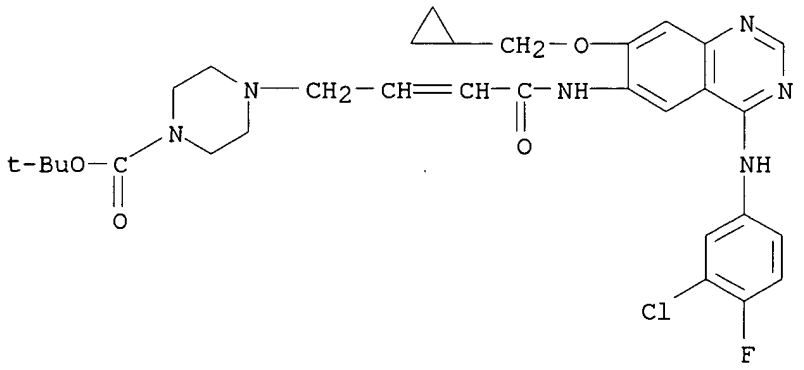
RN 290303-47-8 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

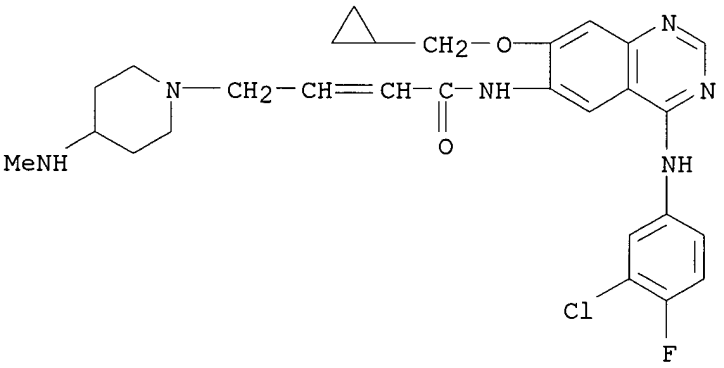


RN 290304-01-7 CAPLUS

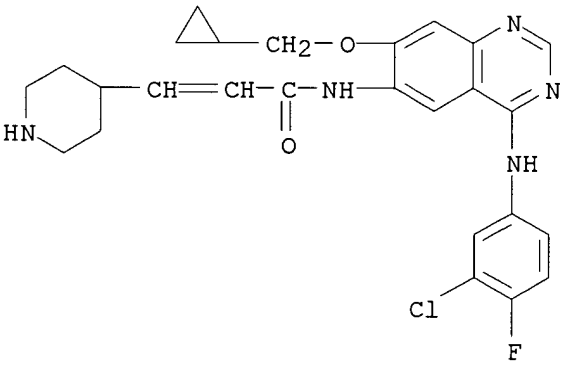
CN 1-Piperazinecarboxylic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 365532-06-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(methylamino)-1-piperidinyl]- (9CI) (CA INDEX NAME)

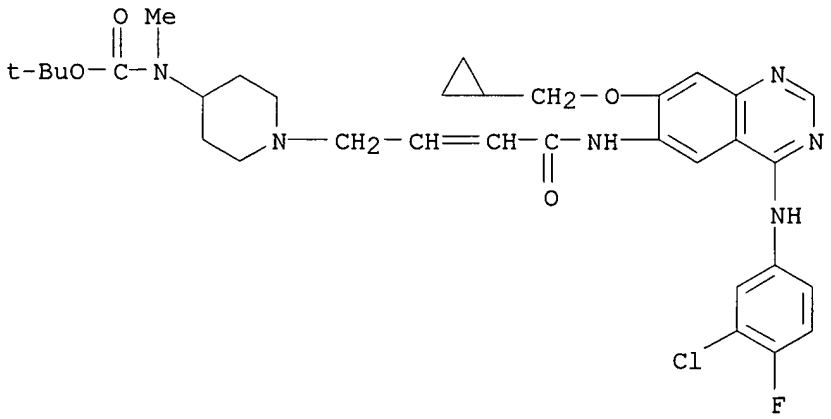


RN 365532-07-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-(4-piperidinyl)- (9CI) (CA INDEX NAME)

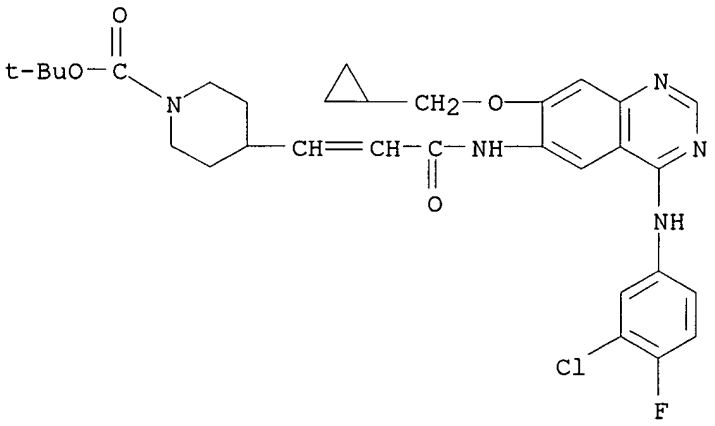


RN 365532-18-9 CAPLUS

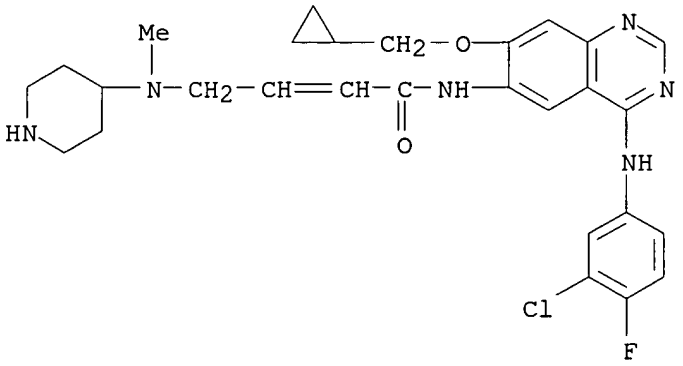
CN Carbamic acid, [1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



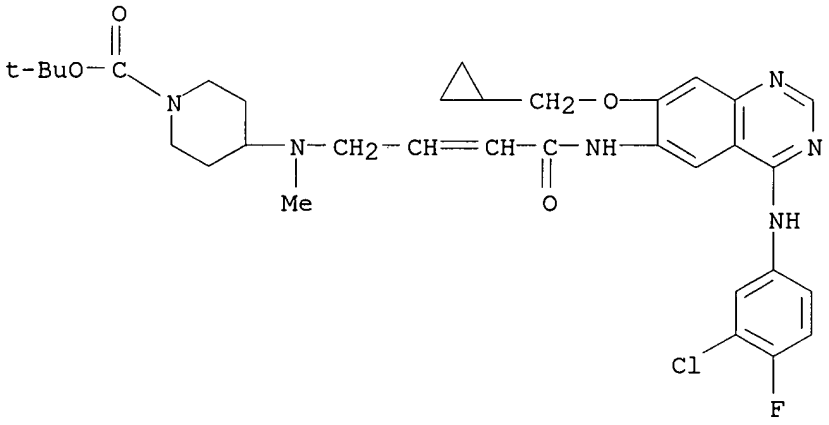
RN 365532-19-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[3-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-3-oxo-1-propenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 367282-36-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(methyl-4-piperidinylamino)- (9CI) (CA INDEX NAME)



RN 367282-44-8 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]methylamino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2001:747043 CAPLUS
DN 135:303901
TI Bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Blech, Stefan; Solca, Flavio
PA Boehringer Ingelheim Pharma KG, Germany
SO Ger. Offen., 28 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 10017539	A1	20011011	DE 2000-10017539	20000408
US 2001044435	A1	20011122	US 2001-816003	20010323
WO 2001077104	A1	20011018	WO 2001-EP3694	20010331
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1280798	A1	20030205	EP 2001-938076	20010331
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DE 2000-10040525 A 20000818
WO 2001-EP3694 W 20010331
OS MARPAT 135:303901
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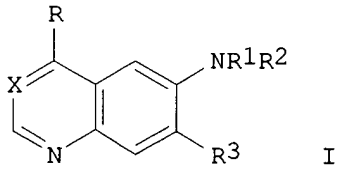

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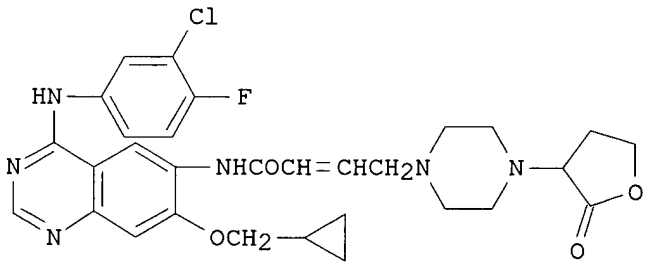


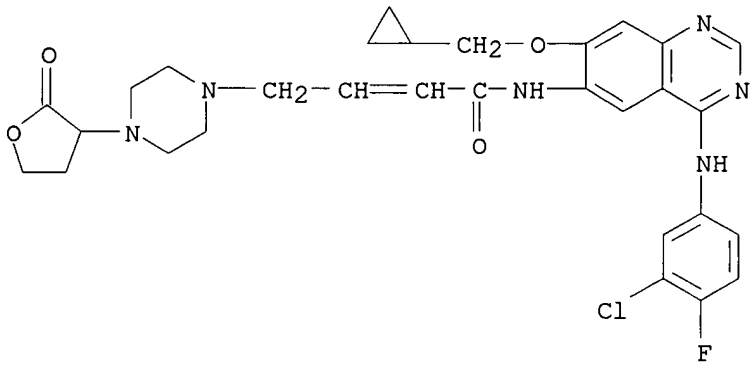
II

AB Bicyclic heterocycles I [X = N, CCN; R = substituted NH2; R1 = H, alkyl; R2 = acyl; R3 = H, (un)substituted alkoxy, cycloalkoxy, tetrahydrofuranyloxy, tetrahydropyranyloxy, tetrahydrofuranylmethoxy, tetrahydropyranylmethoxy] were prepd. for use as inhibitors of tyrosine kinase-mediated signal transduction for treatment of tumors and diseases of the lung and airway. Thus, 4-[(3-chloro-4-fluorophenyl)amino]-7-fluoro-6-nitroquinazoline was treated with cyclopropylmethanol, followed by redn. to the amine, reaction with 4-bromocrotonic acid and N-tert.-butoxycarbonylpiperazine, and deblocking to give the quinazoline II. II had an IC50 for inhibition of epidermal growth factor dependent proliferation of 0.05 nM.

IT **365532-35-0P 365532-39-4P 365532-42-9P 365532-45-2P 365532-47-4P 365532-48-5P 365532-49-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

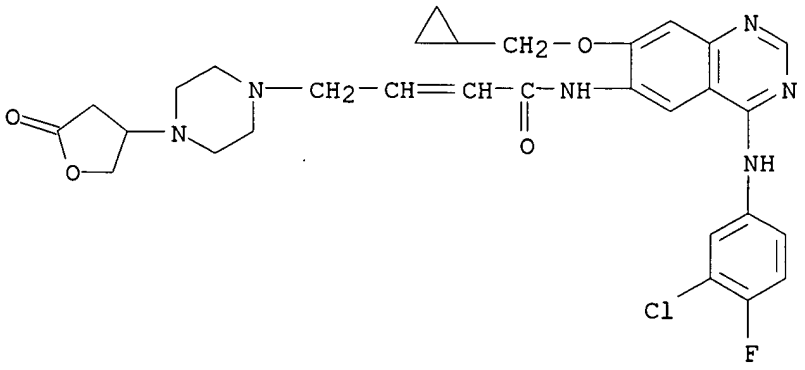
RN 365532-35-0 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)

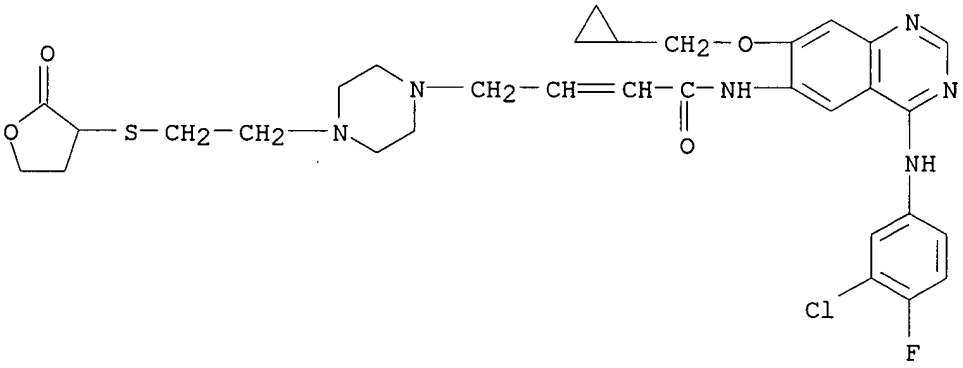


RN 365532-39-4 CAPLUS

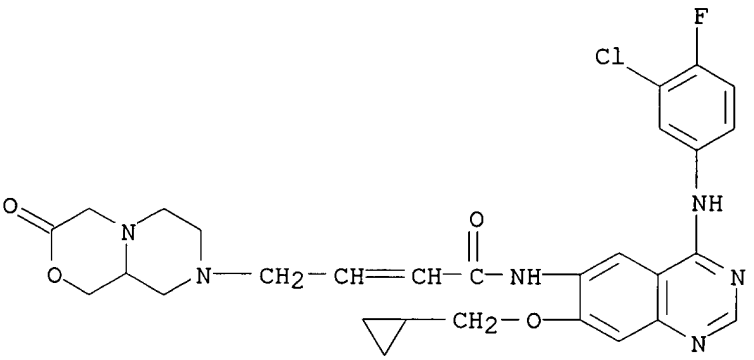
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-5-oxo-3-furanyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)



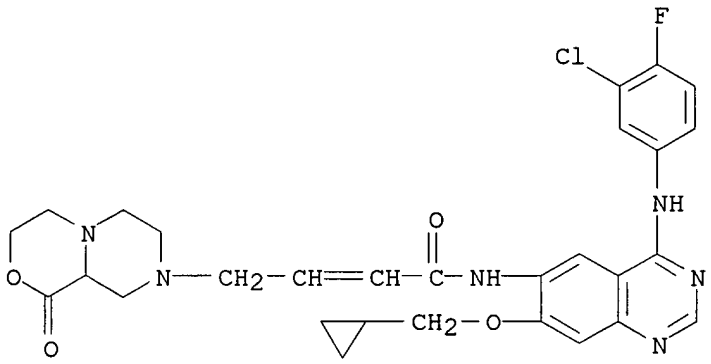
RN 365532-42-9 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[2-[(tetrahydro-2-oxo-3-furanyl)thio]ethyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)



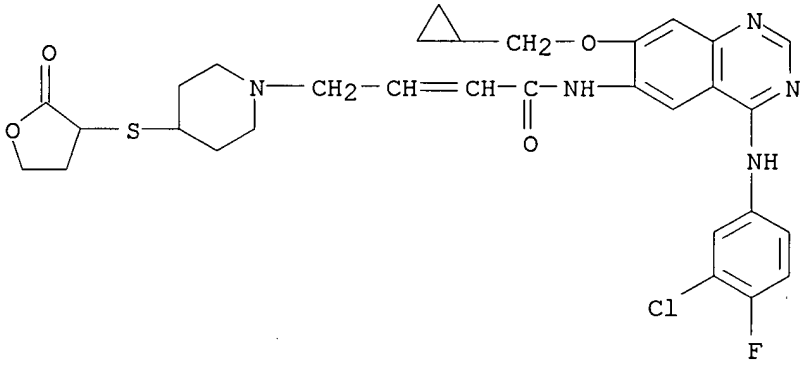
RN 365532-45-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-3-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)- (9CI) (CA INDEX NAME)



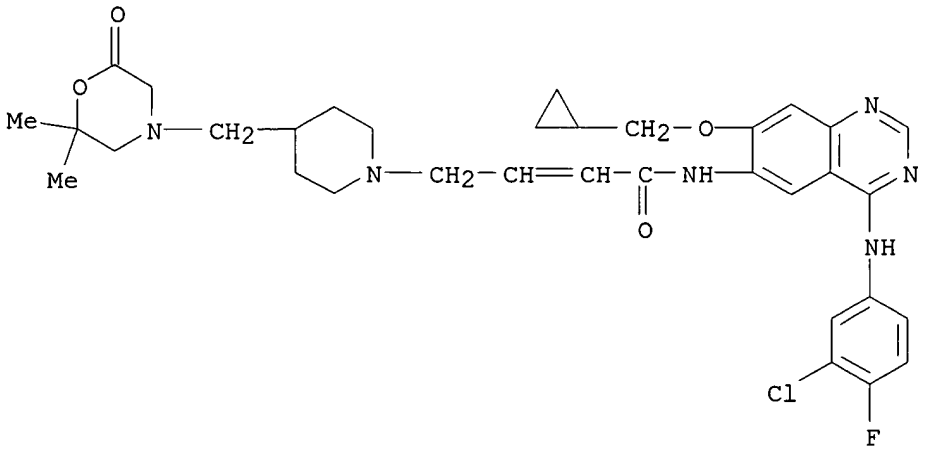
RN 365532-47-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(hexahydro-1-oxopyrazino[2,1-c][1,4]oxazin-8(1H)-yl)- (9CI) (CA INDEX NAME)



RN 365532-48-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(tetrahydro-2-oxo-3-furanyl)thio]-1-piperidinyl]- (9CI) (CA INDEX NAME)



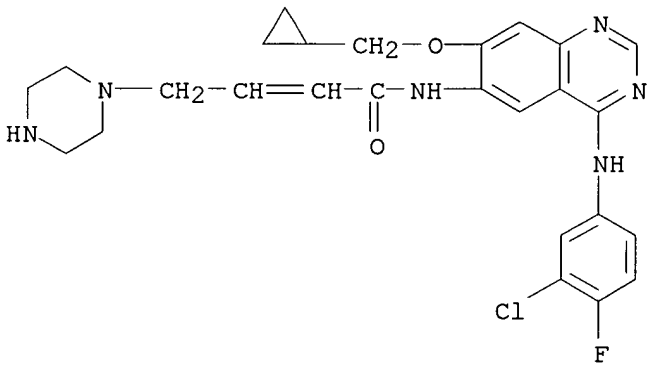
RN 365532-49-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(2,2-dimethyl-6-oxo-4-morpholinyl)methyl]-1-piperidinyl]- (9CI) (CA INDEX NAME)



IT **290303-47-8P 290304-01-7P 365532-06-5P**
365532-07-6P 365532-10-1P 365532-18-9P
365532-19-0P 365532-21-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)

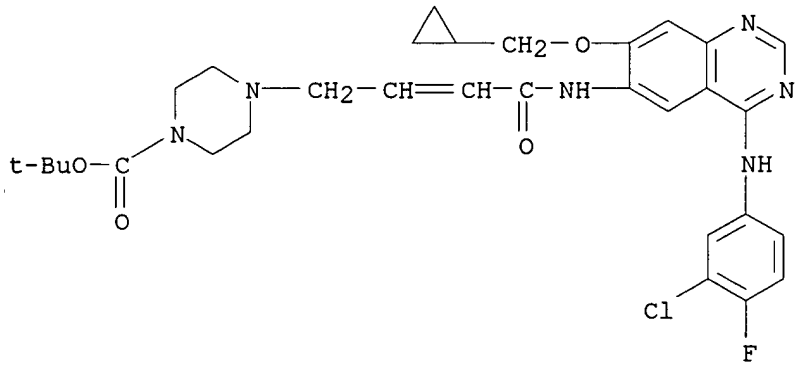
RN 290303-47-8 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

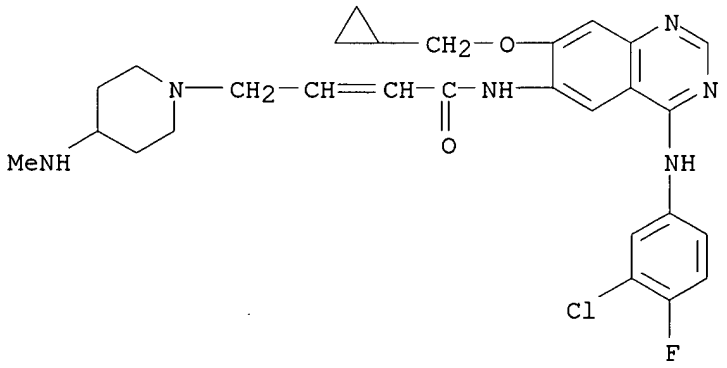


RN 290304-01-7 CAPLUS

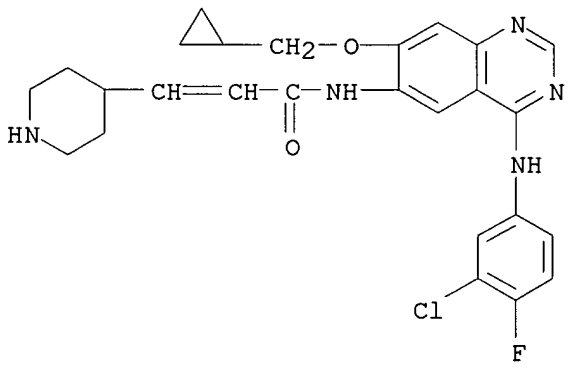
CN 1-Piperazinecarboxylic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 365532-06-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(methylamino)-1-piperidinyl]- (9CI) (CA INDEX NAME)

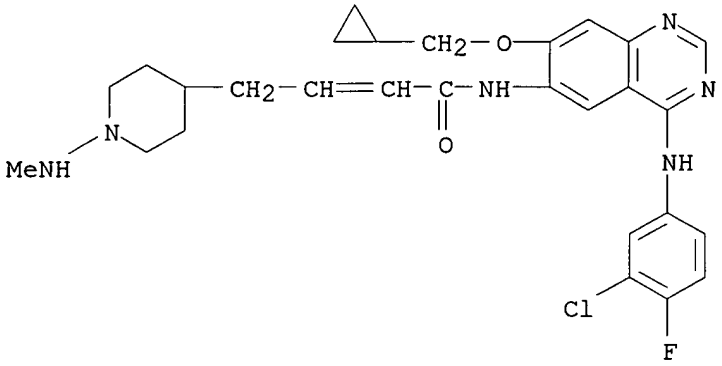


RN 365532-07-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-(4-piperidinyl)- (9CI) (CA INDEX NAME)

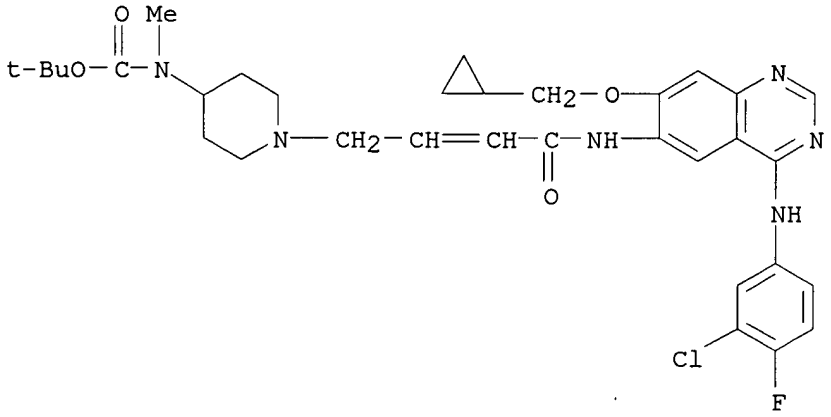


RN 365532-10-1 CAPLUS

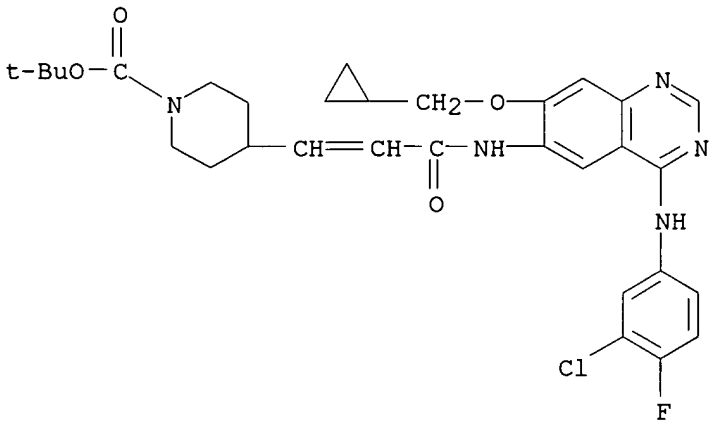
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[1-(methylamino)-4-piperidinyl]- (9CI) (CA INDEX NAME)



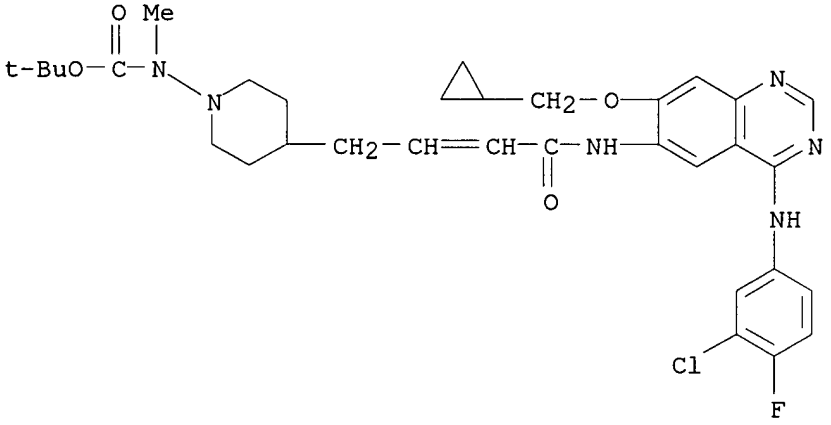
RN 365532-18-9 CAPLUS
CN Carbamic acid, [1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-piperidinyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 365532-19-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 4-[3-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-3-oxo-1-propenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

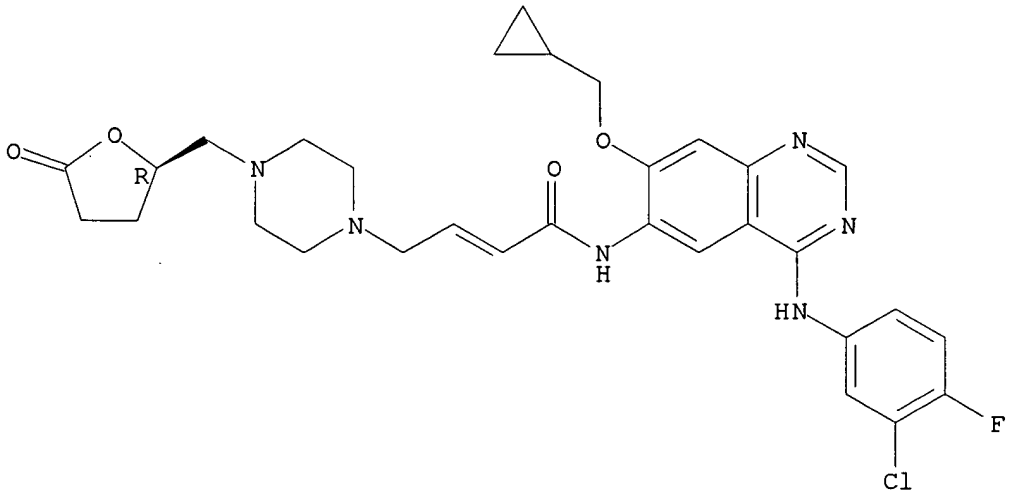


RN 365532-21-4 CAPLUS
CN Carbamic acid, [4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-1-piperidinyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

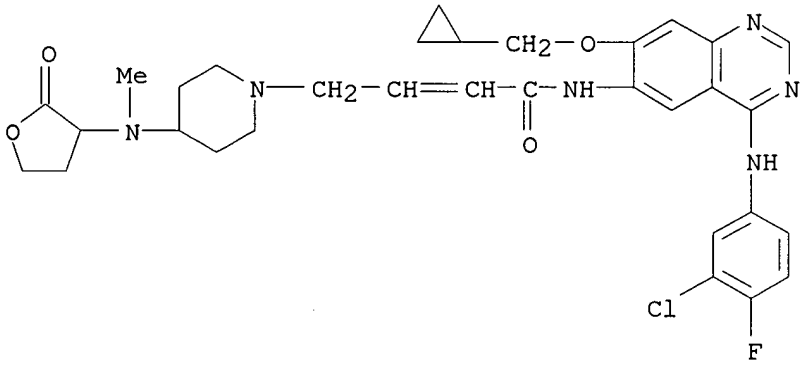


IT **365532-36-1P 365532-37-2P 365532-38-3P**
365532-40-7P 365532-41-8P 365532-43-0P
365532-44-1P 365532-46-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of bicyclic heterocycles as inhibitors of epidermal growth factor receptor mediated signal transduction)
RN 365532-36-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2R)-tetrahydro-5-oxo-2-furanyl]methyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

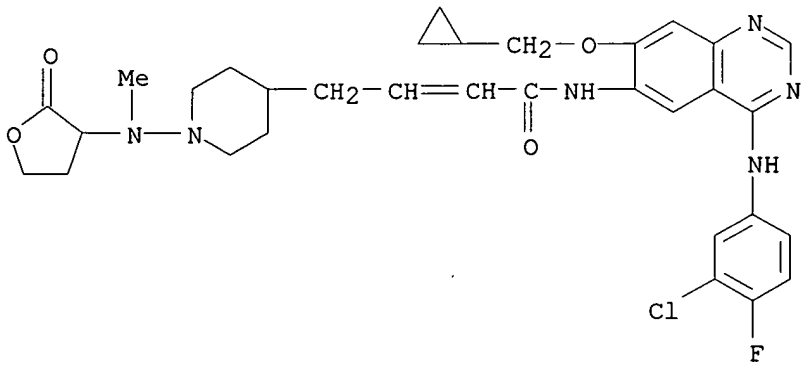
Absolute stereochemistry.
Double bond geometry unknown.



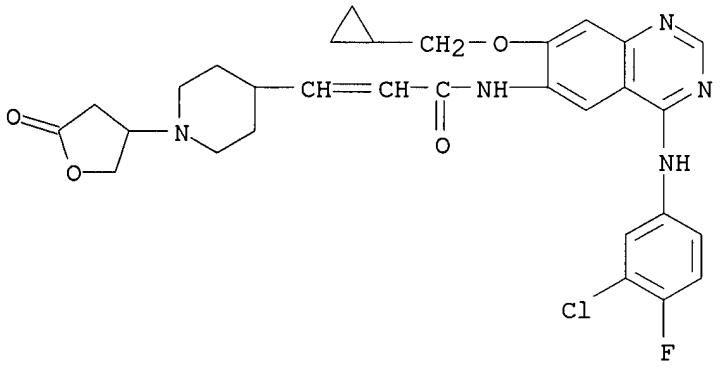
RN 365532-37-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[methyl(tetrahydro-2-oxo-3-furanyl)amino]-1-piperidinyl]- (9CI) (CA INDEX NAME)



RN 365532-38-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[1-[methyl(tetrahydro-2-oxo-3-furanyl)amino]-4-piperidinyl]- (9CI) (CA INDEX NAME)

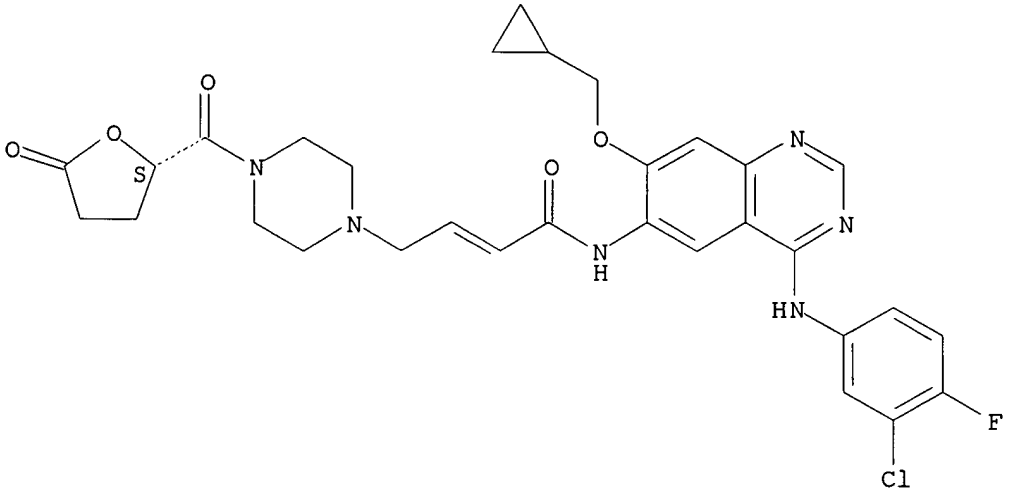


RN 365532-40-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-3-[1-(tetrahydro-5-oxo-3-furanyl)-4-piperidinyl]- (9CI) (CA INDEX NAME)

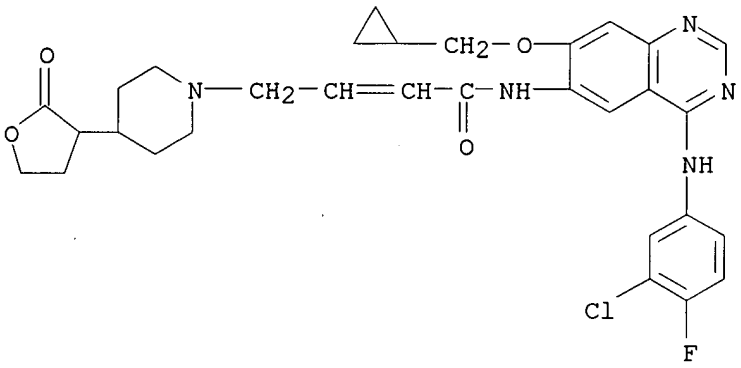


RN 365532-41-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[[(2S)-tetrahydro-5-oxo-2-furanyl]carbonyl]-1-piperazinyl]- (9CI) (CA INDEX NAME)

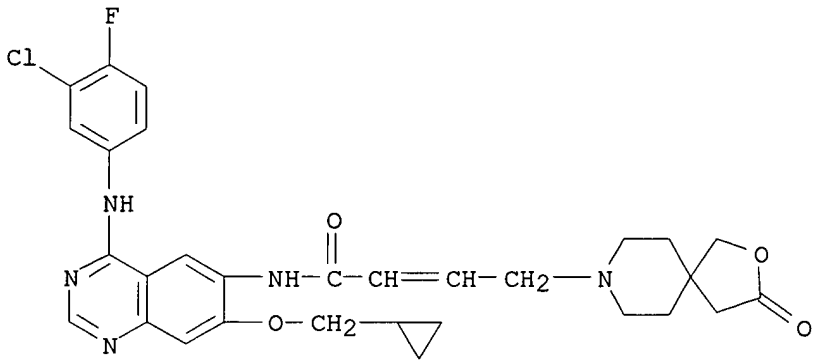
Absolute stereochemistry.
Double bond geometry unknown.



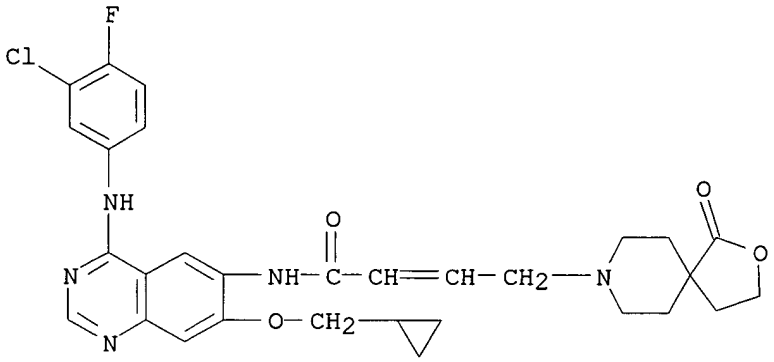
RN 365532-43-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(tetrahydro-2-oxo-3-furanyl)-1-piperidinyl]- (9CI) (CA INDEX NAME)



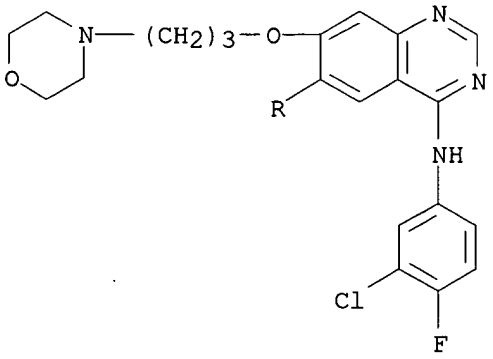
RN 365532-44-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(3-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)

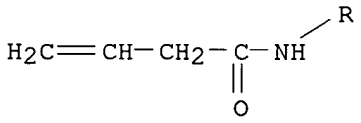


RN 365532-46-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-oxo-2-oxa-8-azaspiro[4.5]dec-8-yl)- (9CI) (CA INDEX NAME)



L17 ANSWER 12 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2001:516932 CAPLUS
DN 135:313144
TI The 4-anilinoquinazoline class of inhibitors of the erbB family of receptor tyrosine kinases
AU Denny, William A.
CS Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SO Farmaco (2001), 56(1-2), 51-56
CODEN: FRMCE8; ISSN: 0014-827X
PB Elsevier Science S.A.
DT Journal
LA English
AB The erbB family of receptor tyrosine kinase enzymes, and particularly EGFR and HER2/neu, have become important targets for potential anticancer drugs. The substrate protein binding site theor. is the more attractive intracellular target on these enzymes, possessing lower homol. than the ATP site between different receptor kinases. However, a major breakthrough in this field was the discovery that 4-anilinoquinazolines are potent and selective inhibitors, despite binding at the ATP site. The very tight structure-activity relationships shown by these compds. suggested a clearly-defined binding mode, where the quinazoline ring binds in the adenine pocket and the anilino ring binds in an adjacent, unique lipophilic pocket. A unique cysteine (Cys-773) adjacent to the quinazoline binding site has prompted the development of irreversible inhibitors that target this residue. Three 4-anilinoquinazoline analogs (two reversible and one irreversible inhibitor) have been evaluated clin. as anticancer drugs. Data from the most advanced, the reversible inhibitor Iressa, suggest that this class of compds. may be of value in cancer chemotherapy.
IT **367518-74-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(4-anilinoquinazoline class of inhibitors of erbB family of receptor tyrosine kinases)
RN 367518-74-9 CAPLUS
CN 3-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)





RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2001:380438 CAPLUS
DN 135:24657
TI Selective cellular targeting: multifunctional delivery vehicles
IN Glazier, Arnold
PA Drug Innovation + Design, Inc., USA
SO PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

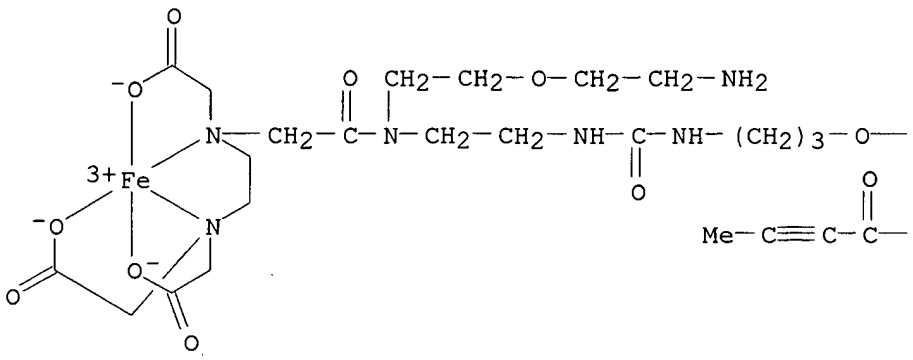
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001036003	A2	20010525	WO 2000-US31262	20001114
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2001016075	A5	20010530	AU 2001-16075	20001114
	EP 1255567	A1	20021113	EP 2000-978631	20001114
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 1999-165485P	P	19991115		
	US 2000-239478P	P	20001011		
	US 2000-241937P	P	20001020		
	WO 2000-US31262	W	20001114		

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

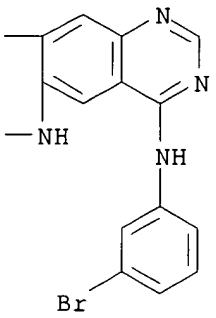
IT **341552-85-0P**
RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

RN 341552-85-0 CAPLUS
CN Iron, [9-[2-(2-aminoethoxy)ethyl]-3,6-bis[(carboxy-.kappa.O)methyl]-8,13-dioxo-17-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-butynyl)amino]-7-quinazolinyl]oxy]-3,6,9,12,14-pentaazaheptadecanoato(3-)-.kappa.N3,.kappa.N6,.kappa.O1]- (9CI) (CA INDEX NAME)

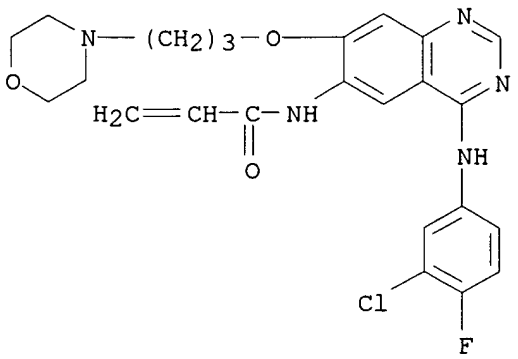
PAGE 1-A



PAGE 1-B



L17 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2001:367797 CAPLUS
DN 135:102151
TI Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in response to ErbB receptor family inhibition
AU Nelson, James M.; Fry, David W.
CS Pfizer Global Research and Development, Ann Arbor, MI, 48105, USA
SO Journal of Biological Chemistry (2001), 276(18), 14842-14847
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The ErbB receptor family is implicated in the malignant transformation of several tumor types and is over-expressed frequently in breast, ovarian, and other tumors. The mechanism by which CI-1033 and gemcitabine, either singly or in combination, kill tumor cells was examd. in two breast lines, MDA-MB-453 and BT474; both overexpress the ErbB-2 receptor. CI-1033, a potent inhibitor of the ErbB family of receptor tyrosine kinases, reduced levels of activated Akt in MDA-MB-453 cells. This effect alone, however, did not induce apoptosis in these cells. Gemcitabine treatment resulted in a moderate increase in the percentage of apoptotic cells that was accompanied by activation of p38 and MAPK (ERK1/2). CI-1033 given 24 h after gemcitabine produced a significant increase in the apoptotic fraction over treatment with either drug alone. During the combined treatment p38 remained activated, whereas Akt and activated MAPK were suppressed. Substitution of CI-1033 with the phosphatidylinositol 3-kinase inhibitor LY294002 and the MAPK/ERK kinase inhibitor PD098059 in combination with gemcitabine produced the same results as the combination of CI-1033 and gemcitabine. P38 suppression by SB203580 prevented the enhanced cell kill by CI-1033. In contrast to MDA-MB-453, BT474 cells exhibited activated p38 under unstressed conditions as well as activated Akt and MAPK. Treatment of BT474 cells with CI-1033 inhibited both the phosphorylation of Akt and MAPK and resulted in a 47% apoptotic fraction. Gemcitabine did not cause apoptosis in the BT474 cells. These data indicate that suppression of Akt and MAPK in the presence of activated p38 results in cell death and a possible mechanism for the enhanced apoptosis produced by the combination of CI-1033 and gemcitabine in MDA-MB-453 cells. Furthermore, tumors that depend on ErbB receptor signaling for survival and exhibit activated p38 in the basal state may be susceptible to apoptosis by CI-1033 as a single agent.
IT **267243-28-7**, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(Akt, MAPK (Erk1/2), and p38 act in concert to promote apoptosis in human breast carcinoma in response to ErbB receptor family inhibition)
RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

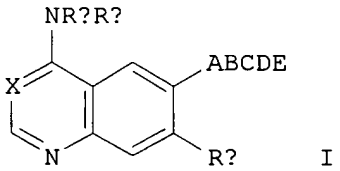


RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 15 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:911231 CAPLUS
DN 134:71599
TI Preparation of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors.
IN Himmelsbach, Frank; Langkopf, Elke; Metz, Thomas; Solca, Flavio; Jung, Birgit; Baum, Anke
PA Boehringer Ingelheim Pharma K.-G., Germany
SO PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000078735	A1	20001228	WO 2000-EP5547	20000616
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	DE 19928281	A1	20001228	DE 1999-19928281	19990621
	DE 10023085	A1	20011115	DE 2000-10023085	20000511
	BR 2000011834	A	20020312	BR 2000-11834	20000616
	EP 1194418	A1	20020410	EP 2000-936888	20000616
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2003502410	T2	20030121	JP 2001-504901	20000616
	EE 200100695	A	20030217	EE 2001-695	20000616
	BG 106189	A	20020830	BG 2001-106189	20011207
	US 2002169180	A1	20021114	US 2001-16280	20011210
	NO 2001006185	A	20011218	NO 2001-6185	20011218
PRAI	DE 1999-19928281	A	19990621		
	US 1999-146644P	P	19990730		
	DE 2000-10023085	A	20000511		
	WO 2000-EP5547	W	20000616		

OS MARPAT 134:71599
GI



I

AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, PhCH2CH2; Rc = (substituted) cycloalkoxy, cycloalkylalkoxy; A = (alkyl-substituted) imino; B = CO, SO2; C = (substituted) allenylene, vinylene, butadienylene, ethynylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, carbonyloxyalkylene, carbonyliminoalkylene, bond, etc.;

E = amino, (substituted) alkylamino, dialkylamino, etc.], were prepd. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propoxy]quinazoline (prepn. given) in CH2Cl2 contg. Et3N at -10.degree. was treated with acryloyl chloride in THF to give 35% 4-[(3-bromophenyl)amino]-7-[3-(1-methylpiperidin-4-yl)propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation of F/L HERC cells with IC50 = <0.35 nM.

IT **314771-08-9P 314771-12-5P 314771-14-7P**
314771-16-9P 314771-17-0P 314771-18-1P
314771-19-2P 314771-20-5P 314771-21-6P
314771-22-7P 314771-23-8P 314771-24-9P
314771-25-0P 314771-26-1P 314771-27-2P
314771-28-3P 314771-29-4P 314771-31-8P
314771-32-9P 314771-33-0P 314771-34-1P
314771-35-2P 314771-36-3P 314771-39-6P
314771-40-9P 314771-41-0P 314771-45-4P
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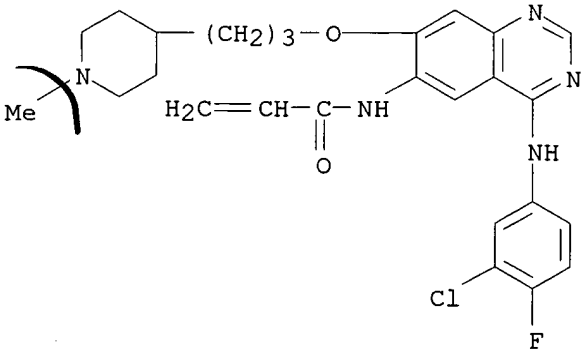
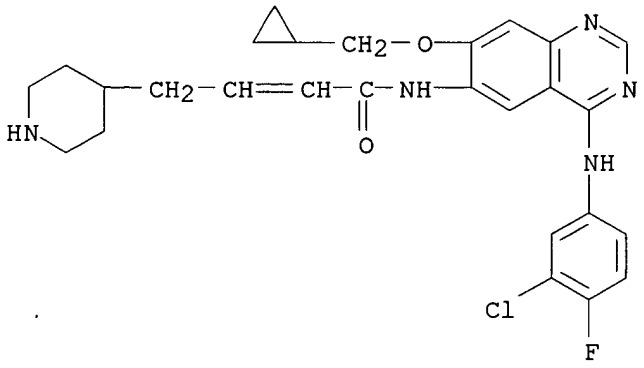
314771-54-5P 314771-55-6P 314771-56-7P
314771-57-8P 314771-58-9P 314771-59-0P
314771-60-3P 314771-64-7P 314771-65-8P
314771-66-9P 314771-67-0P 314771-68-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazolines and aminoquinolines as epidermal growth factor receptor signal transduction inhibitors)

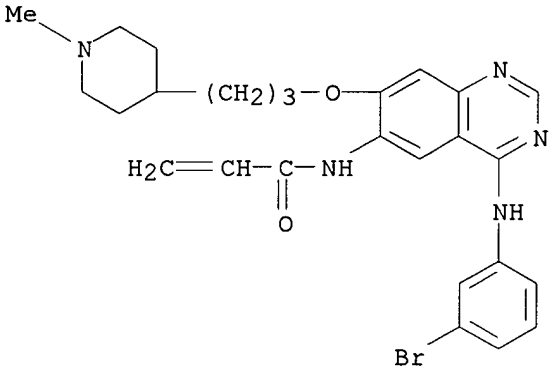
RN 314771-08-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



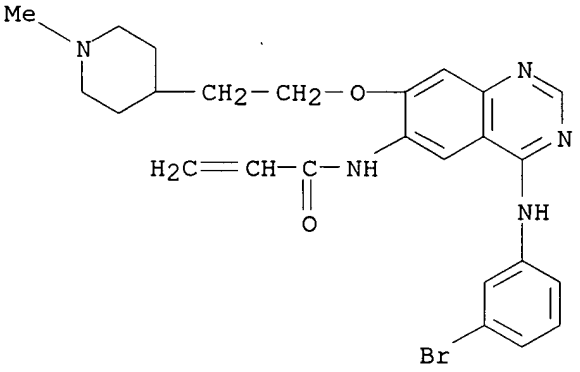
RN 314771-12-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-piperidinyl)- (9CI) (CA INDEX NAME)



RN 314771-14-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

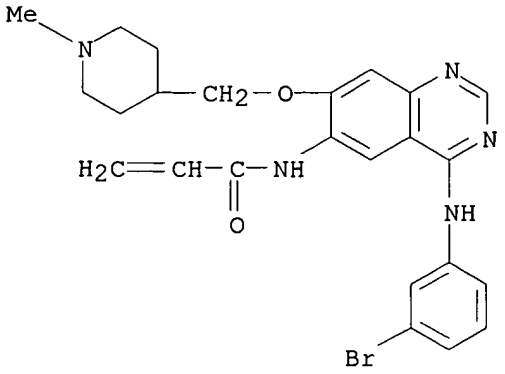


RN 314771-16-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[2-(1-methyl-4-piperidinyl)ethoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

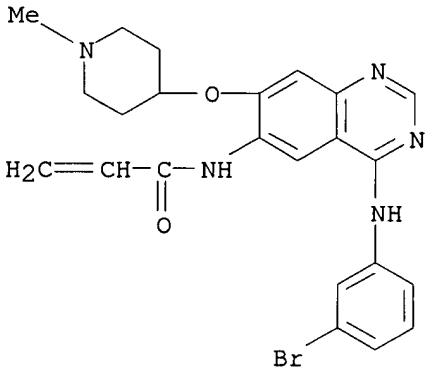


RN 314771-17-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[(1-methyl-4-

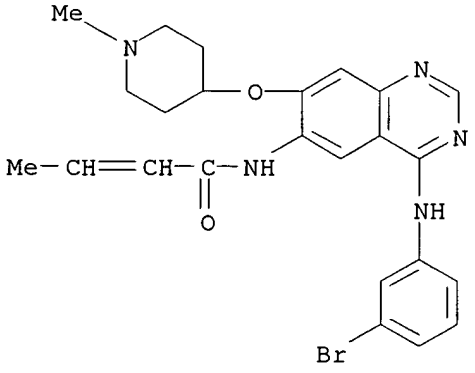
piperidinyl)methoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



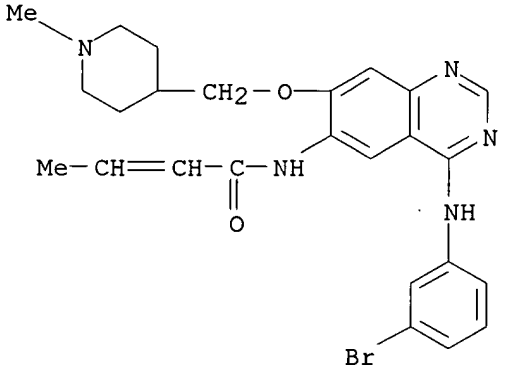
RN 314771-18-1 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[(1-methyl-4-piperidinyl)oxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



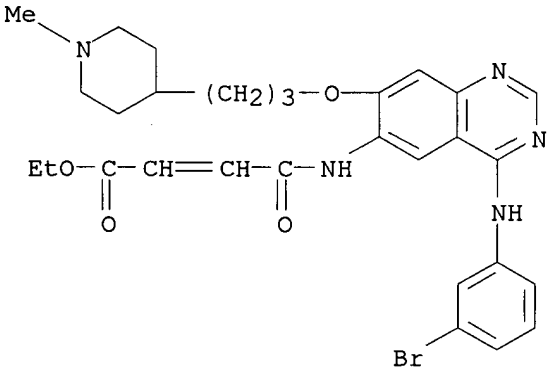
RN 314771-19-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-7-[(1-methyl-4-piperidinyl)oxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 314771-20-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-7-[(1-methyl-4-piperidinyl)methoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

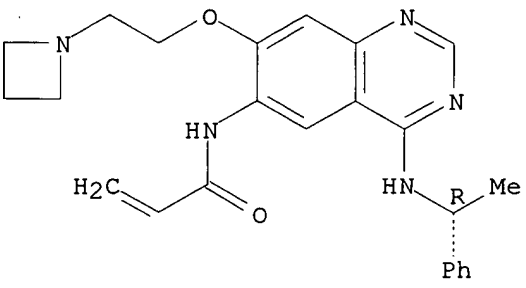


RN 314771-21-6 CAPLUS
CN 2-Butenoic acid, 4-[[4-[(3-bromophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]amino]-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)



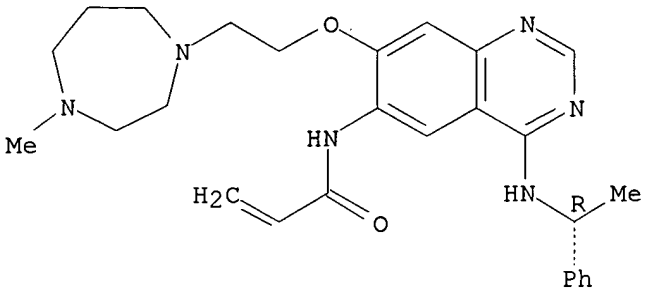
RN 314771-22-7 CAPLUS
CN 2-Propenamide, N-[7-[2-(1-azetidinyl)ethoxy]-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

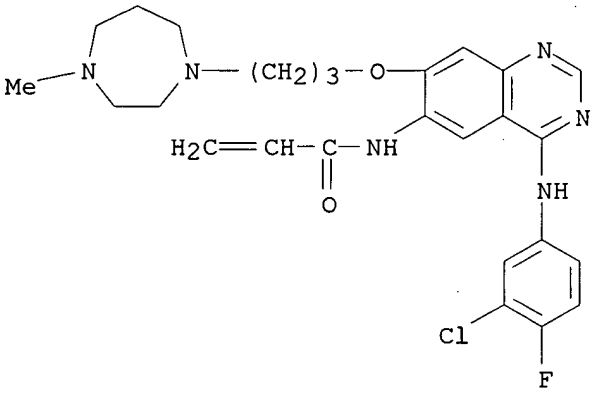


RN 314771-23-8 CAPLUS
CN 2-Propenamide, N-[7-[2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)ethoxy]-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

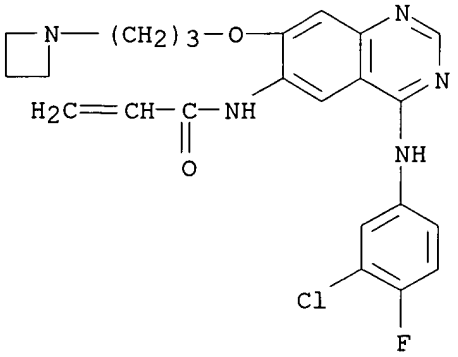
Absolute stereochemistry.



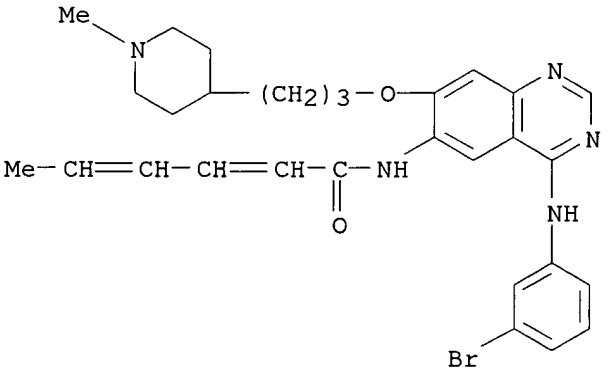
RN 314771-24-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



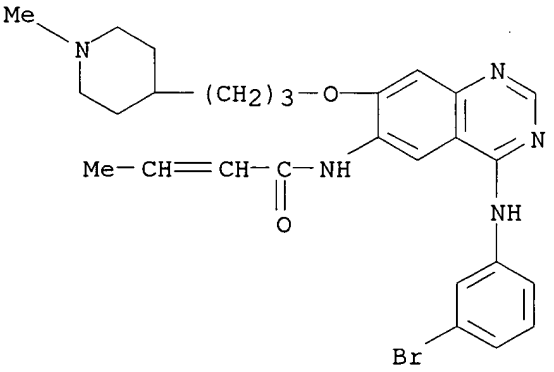
RN 314771-25-0 CAPLUS
CN 2-Propenamide, N-[7-[3-(1-azetidinyl)propoxy]-4-[(3-chloro-4-fluorophenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



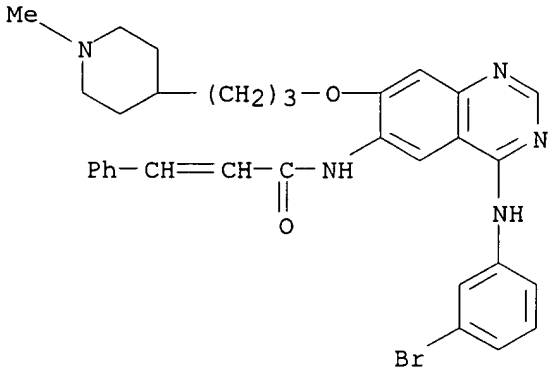
RN 314771-26-1 CAPLUS
CN 2,4-Hexadienamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



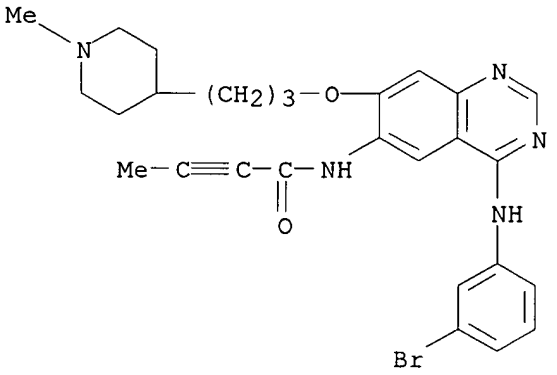
RN 314771-27-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



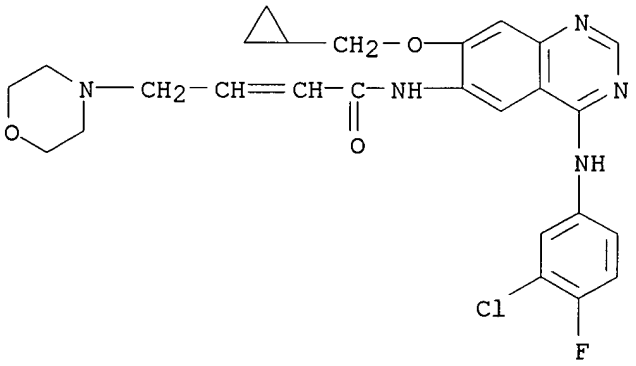
RN 314771-28-3 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]-3-phenyl- (9CI) (CA INDEX NAME)



RN 314771-29-4 CAPLUS
CN 2-Butynamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1-methyl-4-piperidinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

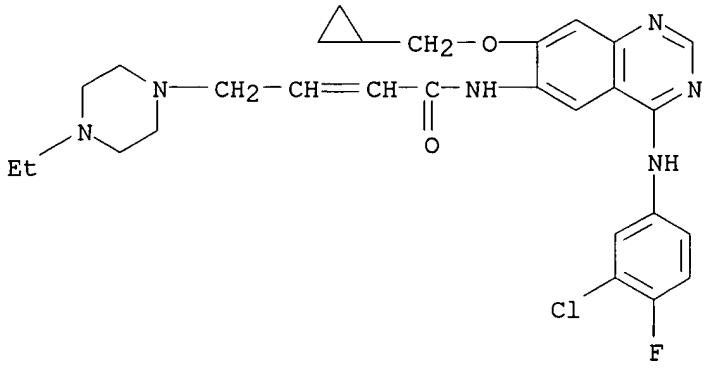


RN 314771-31-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-morpholinyl)- (9CI) (CA INDEX NAME)

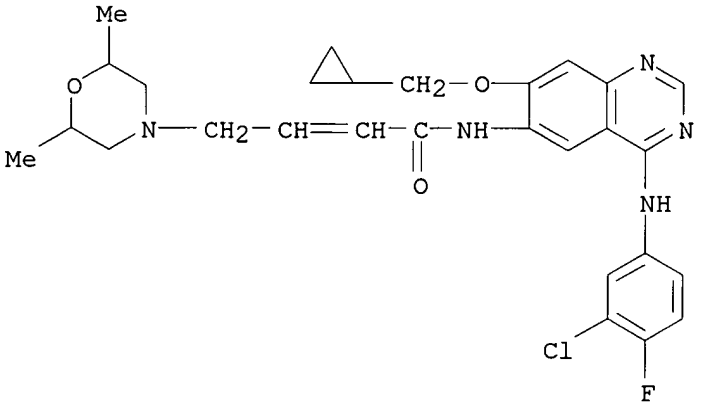


RN 314771-32-9 CAPLUS

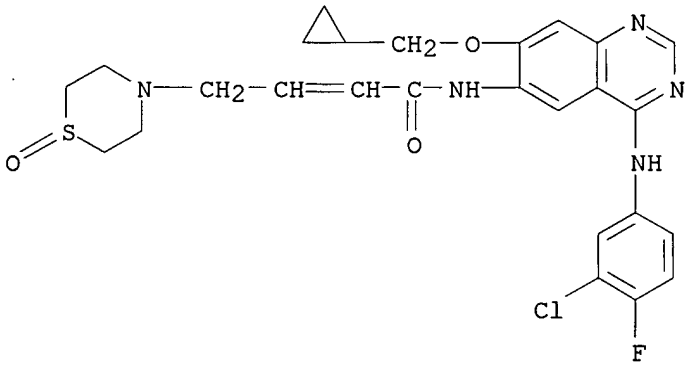
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-ethyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



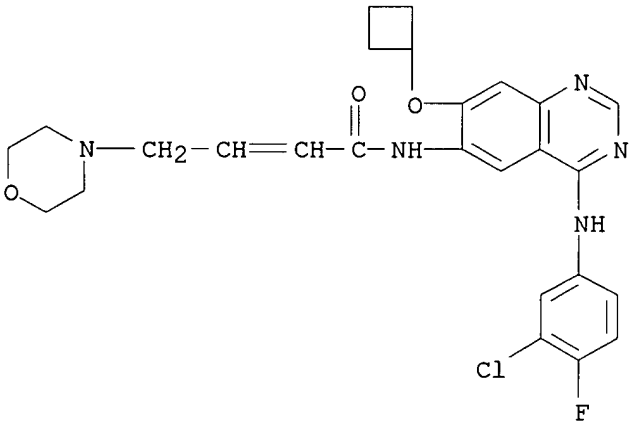
RN 314771-33-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2,6-dimethyl-4-morpholinyl)- (9CI) (CA INDEX NAME)



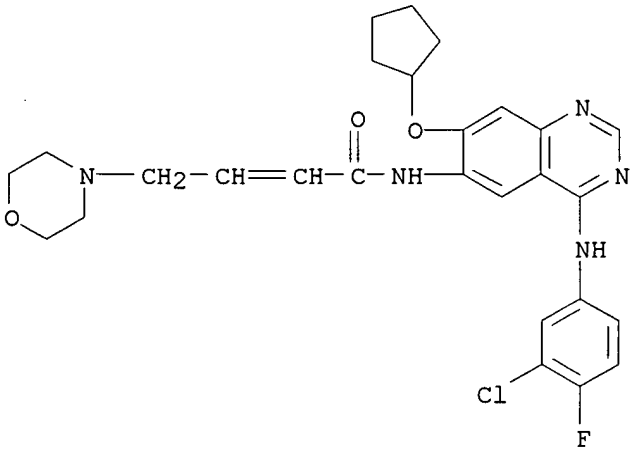
RN 314771-34-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-oxido-4-thiomorpholinyl)- (9CI) (CA INDEX NAME)



RN 314771-35-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]-4-(4-morpholinyl)- (9CI) (CA INDEX NAME)

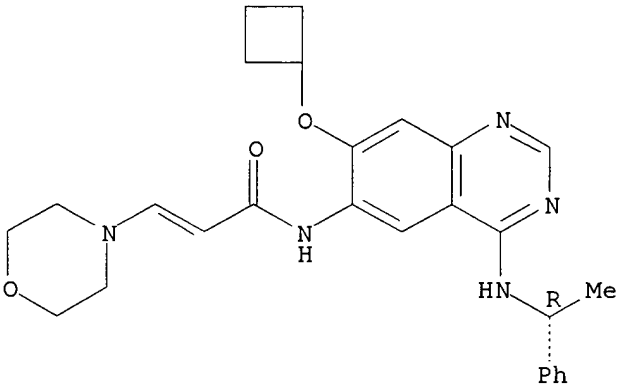


RN 314771-36-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]-4-(4-morpholinyl)- (9CI) (CA INDEX NAME)



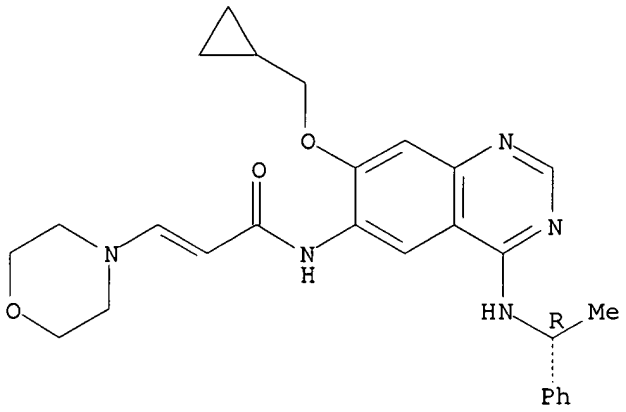
RN 314771-39-6 CAPLUS
CN 2-Propenamide, N-[7-(cyclobutyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



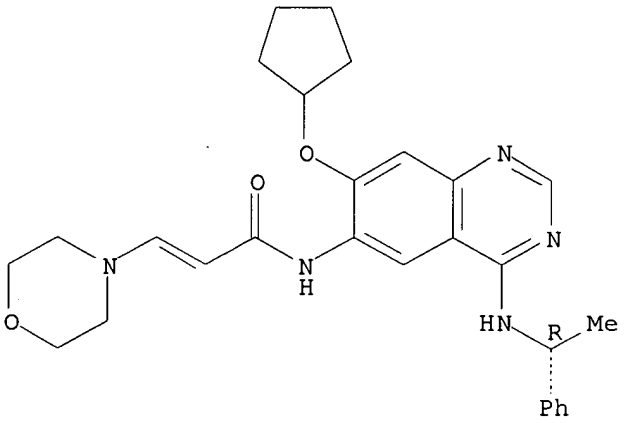
RN 314771-40-9 CAPLUS
CN 2-Propenamide, N-[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

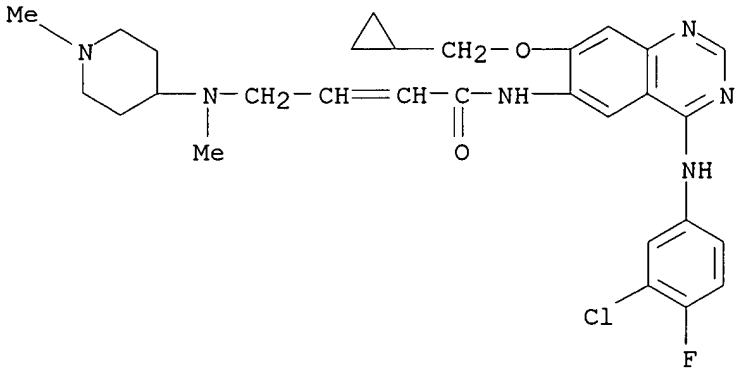


RN 314771-41-0 CAPLUS
CN 2-Propenamide, N-[7-(cyclopentyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]-3-(4-morpholinyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

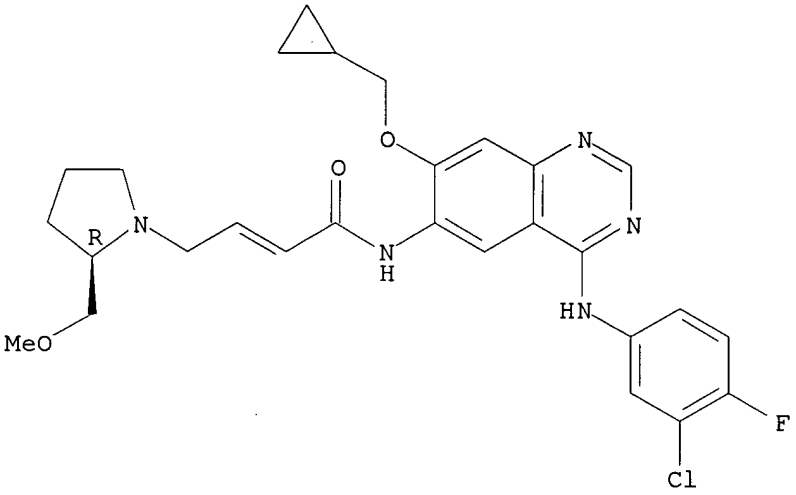


RN 314771-45-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl(1-methyl-4-piperidinyl)amino]- (9CI) (CA INDEX NAME)



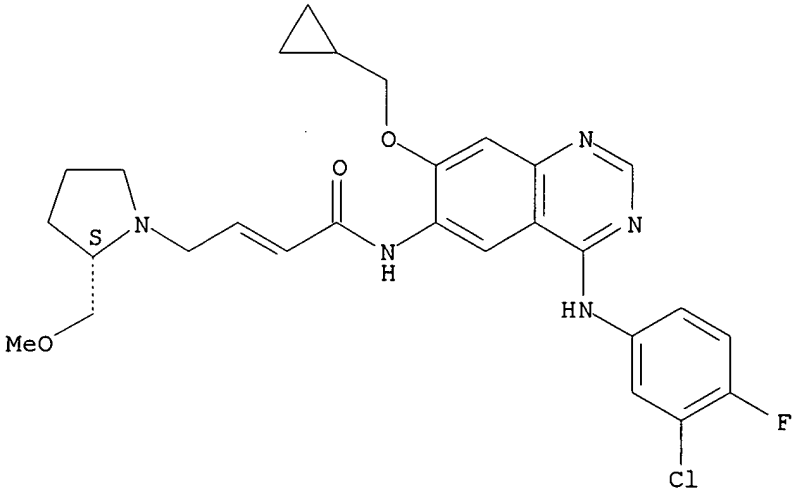
RN 314771-46-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

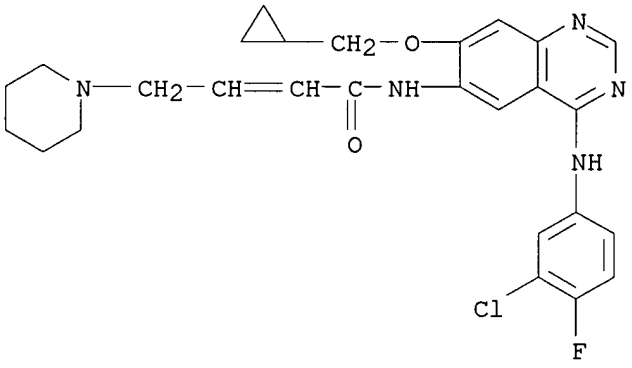


RN 314771-47-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2S)-2-(methoxymethyl)-1-pyrrolidinyl]- (9CI) (CA INDEX NAME)

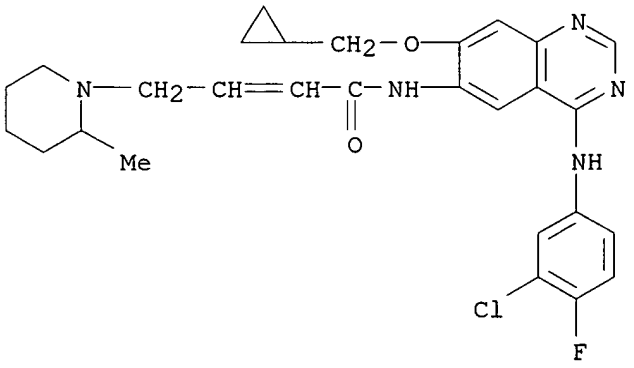
Absolute stereochemistry.
Double bond geometry unknown.



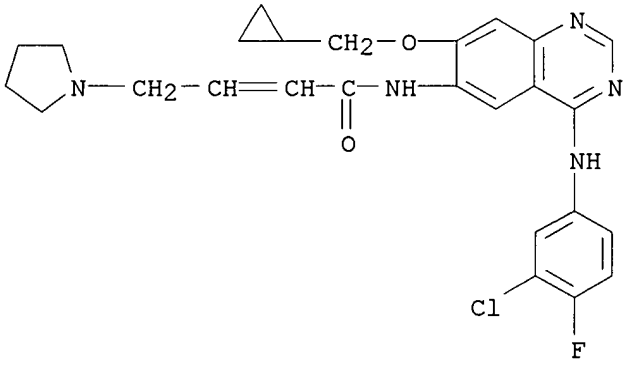
RN 314771-50-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-piperidinyl)- (9CI) (CA INDEX NAME)



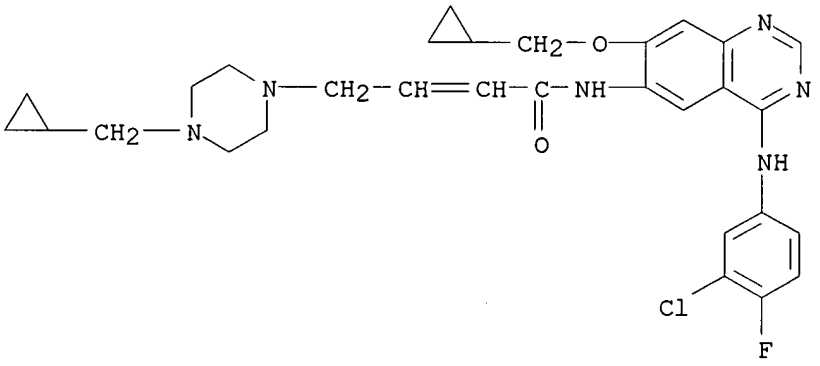
RN 314771-51-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2-methyl-1-piperidinyl)- (9CI) (CA INDEX NAME)



RN 314771-52-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-pyrrolidinyl)- (9CI) (CA INDEX NAME)

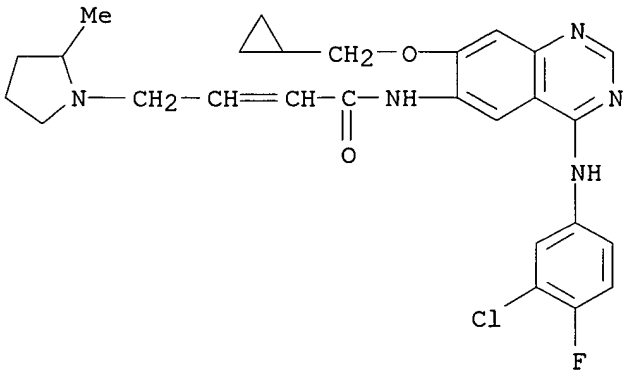


RN 314771-53-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-(cyclopropylmethyl)-1-piperazinyl]- (9CI) (CA INDEX NAME)

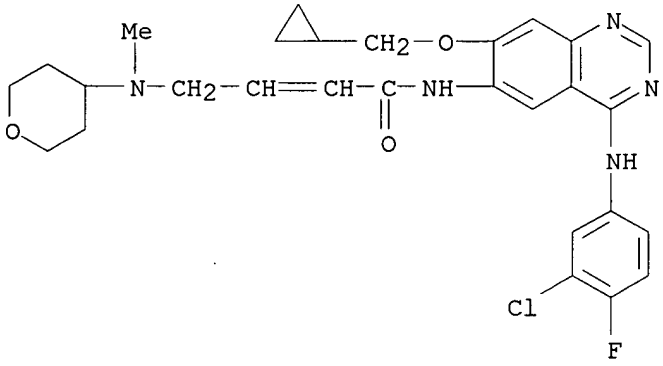


RN 314771-54-5 CAPLUS

CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2-methyl-1-pyrrolidinyl)- (9CI) (CA INDEX NAME)

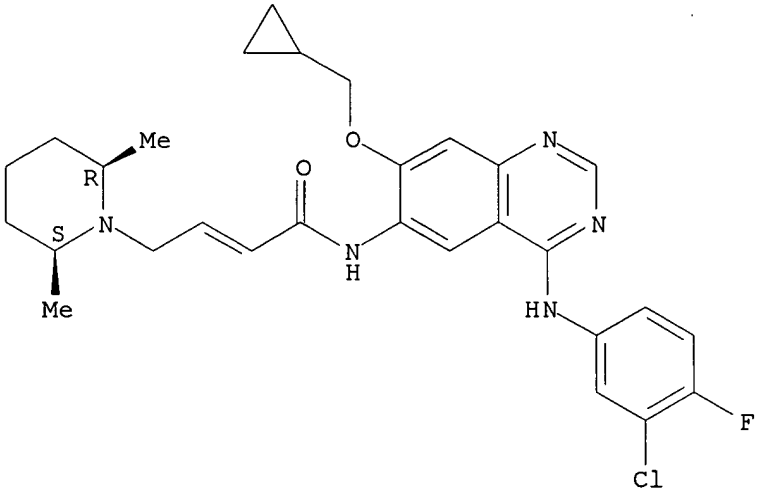


RN 314771-55-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl(tetrahydro-2H-pyran-4-yl)amino]- (9CI) (CA INDEX NAME)

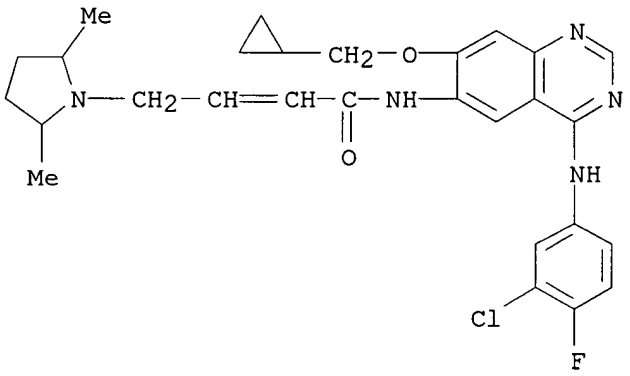


RN 314771-56-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(2R,6S)-2,6-dimethyl-1-piperidinyl]-, rel- (9CI) (CA INDEX NAME)

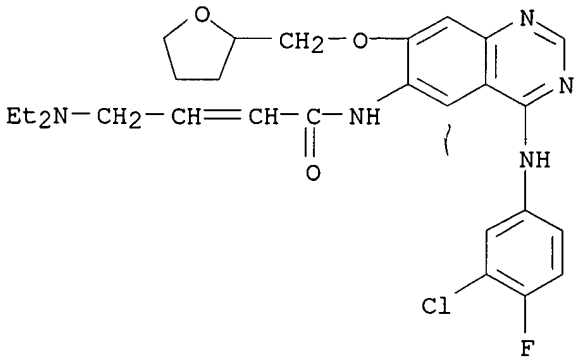
Relative stereochemistry.
Double bond geometry unknown.



RN 314771-57-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2,5-dimethyl-1-pyrrolidinyl)- (9CI) (CA INDEX NAME)

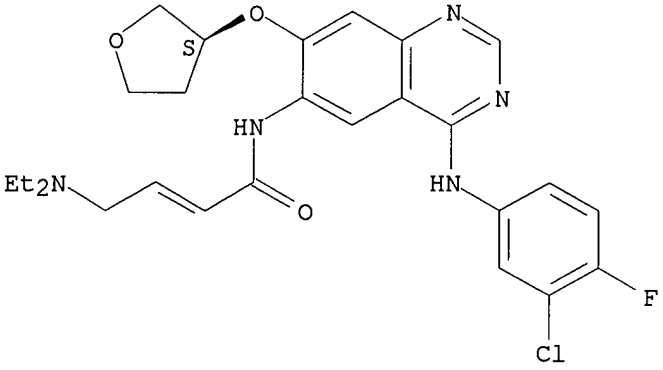


RN 314771-58-9 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2-furanyl)methoxy]-6-quinazolinyl]-4-(diethylamino)- (9CI) (CA INDEX NAME)

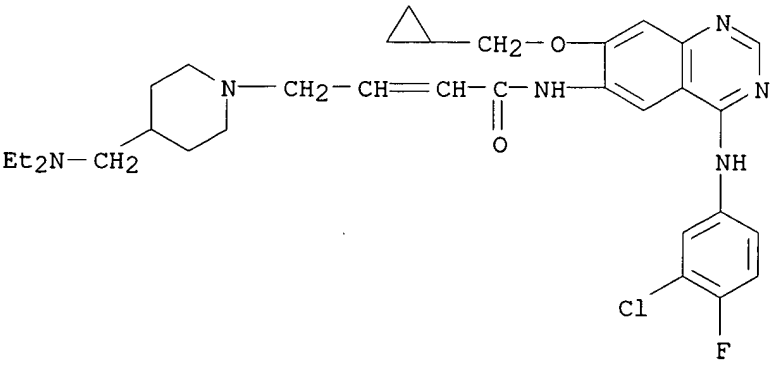


RN 314771-59-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(diethylamino)- (9CI) (CA INDEX NAME)

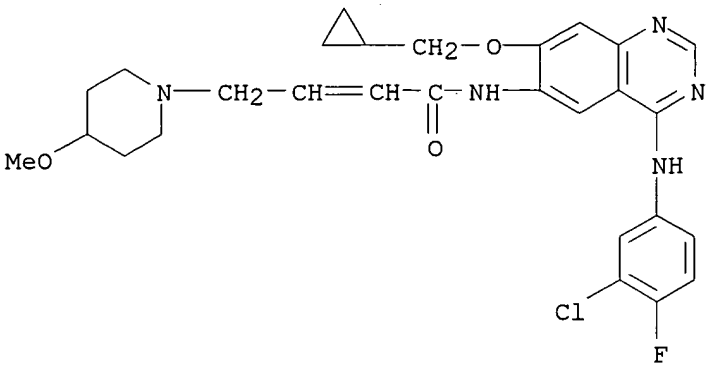
Absolute stereochemistry.
Double bond geometry unknown.



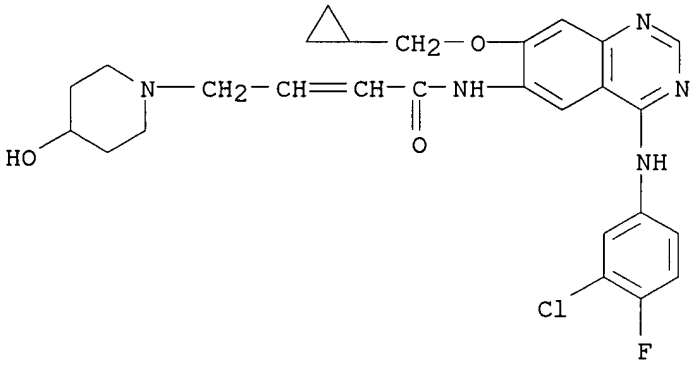
RN 314771-60-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[4-[(diethylamino)methyl]-1-piperidinyl]- (9CI) (CA INDEX NAME)



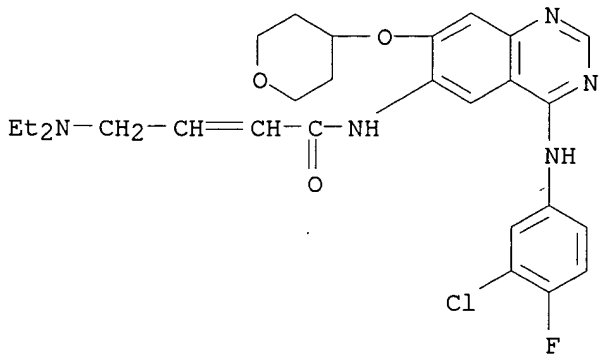
RN 314771-64-7 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-methoxy-1-piperidinyl)- (9CI) (CA INDEX NAME)



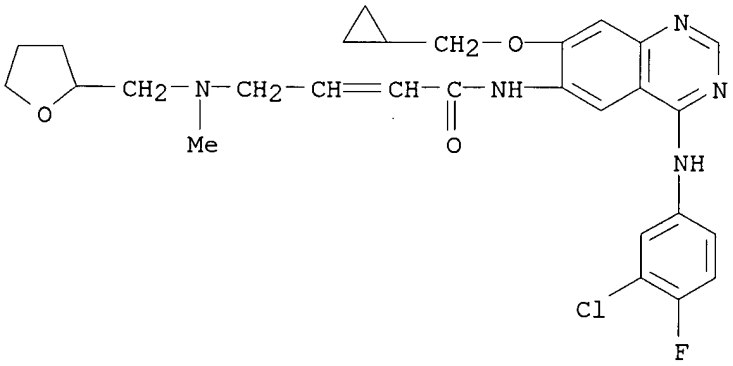
RN 314771-65-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(4-hydroxy-1-piperidinyl)- (9CI) (CA INDEX NAME)



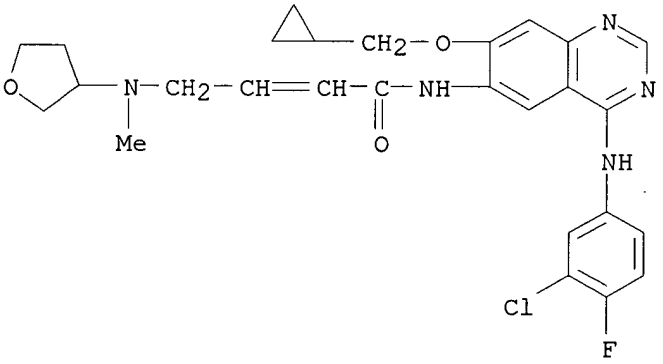
RN 314771-66-9 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[(tetrahydro-2H-pyran-4-yl)oxy]-6-quinazolinyl]-4-(diethylamino)- (9CI) (CA INDEX NAME)



RN 314771-67-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl[(tetrahydro-2-furanyl)methyl]amino]- (9CI) (CA INDEX NAME)



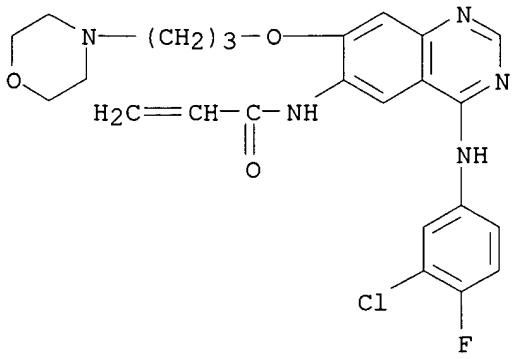
RN 314771-68-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl(tetrahydro-3-furanyl)amino]- (9CI) (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 16 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:828300 CAPLUS
DN 135:57892
TI Radiosensitization of human breast cancer cells by a novel ErbB family receptor tyrosine kinase inhibitor
AU Rao, G. S.; Murray, S.; Ethier, S. P.
CS Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA
SO International Journal of Radiation Oncology, Biology, Physics (2000), 48(5), 1519-1528
CODEN: IOBPD3; ISSN: 0360-3016
PB Elsevier Science Inc.
DT Journal
LA English
AB Purpose: Overexpression of the ErbB family of growth factor receptors is present in a wide variety of human tumors and is correlated with poor prognosis. The purpose of this study was to det. the effects of a novel small mol. ErbB tyrosine kinase inhibitor, CI-1033, in combination with ionizing radiation on breast cancer cell growth and survival. Materials & Methods: Growth assays were performed on ErbB-overexpressing human breast cancer cells developed in our lab. in the presence of 0.1-1.0 .mu.M CI-1033 (Parke Davis). Clonogenic survival assays were performed in the presence of ionizing radiation with or without CI-1033. For some expts., clonogen nos., defined as the product of surviving fraction and total no. of cells, were calcd. at each time point during a course of multifraction radiation. Results: CI-1033 potently inhibited the growth of ErbB-overexpressing breast cancer cells. A single 48-h exposure of 1 .mu.M CI-1033 resulted in growth inhibition for 7 days, whereas three times weekly administration resulted in sustained growth inhibition. Clonogenic survival was modestly decreased after a 7-day exposure to CI-1033. Exposure to both CI-1033 and radiation (6 Gy) yielded a 23-fold decrease in clonogenic survival compared to radiation alone. In a multifraction expt., exposure to CI-1033 and three 5-Gy fractions of gamma radiation decreased the total no. of clonogens in the population by 65-fold compared to radiation alone. Conclusion: CI-1033 results in potent growth inhibition and modest cytotoxicity of ErbB-overexpressing breast cancer cells, and has synergistic effects when combined with ionizing radiation. These data suggest that CI-1033 may have excellent clin. potential both alone and in combination with radiation therapy.
IT **267243-28-7**, CI-1033
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(radiosensitization of human breast cancer cells by ErbB family receptor tyrosine kinase inhibitor)
RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:628125 CAPLUS
DN 133:207919
TI Preparation of 4-amino-quinazoline and quinoline derivatives having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas; Solca, Flavio; Blech, Stefan
PA Boehringer Ingelheim Pharma K.-G., Germany
SO PCT Int. Appl., 232 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000051991	A1	20000908	WO 2000-EP1496	20000224
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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	DE 19911366	A1	20000921	DE 1999-19911366	19990315
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	DE 19954816	A1	20010517	DE 1999-19954816	19991113
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	EP 1157011	A1	20011128	EP 2000-910695	20000224
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	BR 2000008524	A	20011218	BR 2000-8524	20000224
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	BG 105765	A	20020329	BG 2001-105765	20010801
	NO 2001004114	A	20011015	NO 2001-4114	20010824
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	WO 2000-EP1496	W	20000224		

OS MARPAT 133:207919
GI

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C07D 239/94, 215/54, A61K 31/517, 31/4706, A61P 35/00, C07F 9/40, C07D 401/12, 493/12, 403/12, 405/12, 413/12

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(11) International Publication Number: WO 00/51991

(43) International Publication Date: 8 September 2000 (08.09.00)

not prior art

(21) International Application Number: PCT/EP00/01496

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(30) Priority Data:

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199 11 366.1	15 March 1999 (15.03.99)	DE
199 28 306.0	21 June 1999 (21.06.99)	DE
60/149,329	17 August 1999 (17.08.99)	US
199 54 816.1	13 November 1999 (13.11.99)	DE

(71) Applicant *(for all designated States except US)*: BOEHRINGER INGELHEIM PHARMA KG [DE/DE]; D–55216 Ingelheim/Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: HIMMELSBACH, Frank [DE/DE]; Ahornweg 16, D–88441 Mittelbiberach (DE). LANGKOPF, Elke [DE/DE]; Schloss 3, D–88447 Warthausen (DE). JUNG, Birgit [DE/DE]; Mühlstrasse 23, D–55270 Schwabenheim (DE). METZ, Thomas [DE/AT]; Traungasse 6/5, A–1030 Vienna (AT). SOLCA, Flavio [CH/AT]; Fimbingergasse 1/9, A–1230 Vienna (AT). BLECH, Stefan [DE/DE]; Müllerweg 9, D–88447 Warthausen (DE).

(74) Agent: LAUDIEN, Dieter; Boehringer Ingelheim GmbH, Corporate Patent Division, D–55216 Ingelheim/Rhein (DE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

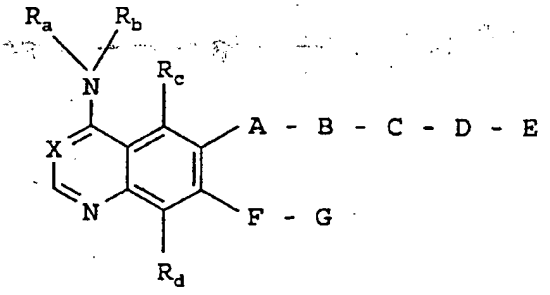
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 4–AMINO–QUINAZOLINE AND QUINOLINE DERIVATIVES HAVING AN INHIBITORY EFFECT ON SIGNAL TRANsSDUCTION MEDIATED BY TYROSINE KINASES

(57) Abstract

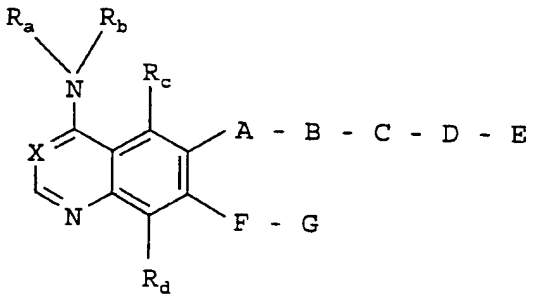
The present invention relates to bicyclic heterocycles of general formula (I), wherein R_a to R_d, A to G and X are defined as in claim 1, the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases, their use for treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory tract, and the preparation thereof.



(I)

Patent Claims

1. Bicyclic heterocycles of general formula



, (I)

wherein

R_a denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, whilst

R_1 and R_2, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4}-alkyl, hydroxy, C_{1-4}-alkoxy, C_{3-6}-cycloalkyl, C_{4-6}-cycloalkoxy, C_{2-5}-alkenyl or C_{2-5}-alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C_{3-5}-alkenyloxy or C_{3-5}-alkynyloxy group, wherein the unsaturated moiety may not be linked to the oxygen atom,

a C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, C_{1-4}-alkylsulphonyloxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C_{1-4}-alkyl groups, wherein the substituents may be identical or different, or

R_1 together with R_2, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH, -CH=CH-NH or -CH=N-NH group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group,

R_c and R_d, which may be identical or different, in each case denote a hydrogen, fluorine or chlorine atom, a methoxy group, or a methyl group optionally substituted by a methoxy, dimethylamino, diethylamino, pyrrolidino, piperidino or morpholino group,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an oxygen atom or an imino group optionally substituted by a C_{1-4}-alkyl group,

B denotes a carbonyl or sulphonyl group,

C denotes a 1,3-allenylene, 1,1 or 1,2-vinylene group which may be substituted in each case by one or two methyl groups or by a trifluoromethyl group,

an ethynylene group or

a 1,3-butadien-1,4-ylene group optionally substituted by 1 to 4 methyl groups or by a trifluoromethyl group,

D denotes an alkylene, -CO-alkylene or -SO_2-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms and additionally 1 to 4 hydrogen atoms in the alkylene moiety may be replaced by fluorine atoms, while the linking of the -CO-alkylene and -SO_2-alkylene group to the adjacent group C in each case must take place via the carbonyl or sulphonyl group,

a -CO-O-alkylene, -CO-NR_4-alkylene or -SO_2-NR_4-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms, whilst the linking to the adjacent group C in each case must take place via the carbonyl or sulphonyl group, wherein

R_4 denotes a hydrogen atom or a C_{1-4}-alkyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond,

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5-group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group, which may be substituted by an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9) group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups, which may be terminally substituted in each case by a C_{1-6}-alkylcarbonylsulphenyl, C_{3-7}-cycloalkylcarbonylsulphenyl, C_{3-7}-cycloalkyl-C_{1-3}-alkylcarbonylsulphenyl, arylcarbonylsulphenyl or aryl-C_{1-3}-alkylcarbonylsulphenyl group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted in each case by a C_{1-6}-alkylcarbonyloxy, C_{3-7}-cycloalkylcarbonyloxy, C_{3-7}-cycloalkyl-C_{1-3}-alkylcarbonyloxy, arylcarbonyloxy or aryl-C_{1-3}-alkylcarbonyloxy group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups, each of which may be terminally substituted by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group, which may be substituted by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{4-7}-cycloalkyl group optionally substituted by 1 or 2 methyl groups,

a C_{3-5}-alkenyl or C_{3-5}-alkynyl group, wherein the unsaturated moiety may not be linked to the oxygen atom,

a C_{3-7}-cycloalkyl-C_{1-4}-alkyl, aryl, aryl-C_{1-4}-alkyl or R_gCO-O-(R_eCR_f)-group, whilst

R_e and R_f, which may be identical or different, each denote a hydrogen atom or a C_{1-4}-alkyl group and

R_g denotes a C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{1-4}-alkoxy or C_{5-7}-cycloalkoxy group,

and R_9 denotes a C_{1-4}-alkyl, aryl or aryl-C_{1-4}-alkyl group,

a 4- to 7-membered alkyleneimino group which may be substituted by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6OCO or R_6OCO-C_{1-4}-alkyl groups or by an R_6OCO-group and an R_6OCO-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined and

R_{10} denotes a hydrogen atom, a C_{1-4}-alkyl, formyl, C_{1-4}-alkylcarbonyl or C_{1-4}-alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at cyclic carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group and additionally at cyclic carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings are additionally substituted in each case at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a morpholino or thiomorpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino or thiomorpholino group which is substituted in the 2 and 6 position in each case by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5-group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is in each case terminally substituted by a

di-(C_{1-4}-alkoxy)-methyl or tri-(C_{1-4}-alkoxy)-methyl group, while R_5 is as hereinbefore defined,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is in each case terminally substituted by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl group optionally substituted by one or two methyl groups, while R_5 is as hereinbefore defined,

an $R_{11}NR_5$ group wherein R_5 is as hereinbefore defined and

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl, 2-oxo-tetrahydropyran-5-yl, 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group optionally substituted by one or two methyl groups,

an amino group or an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups wherein the alkyl groups may be identical or different and each alkyl moiety may be substituted from position 2 onward by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, or by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups wherein in each case a methylene group in the 4 position is replaced by an oxygen or sulphur atom, by

an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, whilst R_{10} is as hereinbefore defined,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

or D together with E denotes a hydrogen, fluorine or chlorine atom,

a C_{1-4}-alkyl group optionally substituted by 1 to 5 fluorine atoms,

a C_{3-6}-cycloalkyl group,

an aryl, heteroaryl, C_{1-4}-alkylcarbonyl, arylcarbonyl, carboxy, C_{1-4}-alkoxycarbonyl, $R_gCO-O-(R_eCR_f)-O-CO$, $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$-group wherein R_e to R_g and R_7 to R_9 are as hereinbefore defined,

an aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-$(C_{1-4}$-alkyl)-aminocarbonyl group or

a carbonyl group, which is substituted by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, while R_{10} is as hereinbefore defined,

F denotes a C_{1-6}-alkylene group, an -O-C_{1-6}-alkylene group, whilst the alkylene moiety is linked to the group G, or an

oxygen atom, whilst the latter may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5-group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein R_5 to R_9 are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4}-alkyl, R_6O-CO-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, wherein R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are each linked to a carbon atom of the group F,

a morpholino or thiomorpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino or thiomorpholino group which is substituted in the 2 and 6 positions by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5-group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is in each case terminally substituted by a di-(C_{1-4}-alkoxy)-methyl or tri-(C_{1-4}-alkoxy)-methyl group, wherein R_5 is as hereinbefore defined,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is in each case terminally substituted by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl group optionally

substituted by one or two methyl groups, wherein R_5 is as hereinbefore defined,

a R_hNR_5-group wherein R_5 is as hereinbefore defined and R_h denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two methyl groups,

an amino group or an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups wherein the alkyl groups may be identical or different and each alkyl moiety may be substituted from position 2 onward by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a 4- to 7-membered alkyleneimino group optionally substituted by 1 to 4 methyl groups,

a 6- to 7-membered alkyleneimino group optionally substituted by 1 or 2 methyl groups wherein in each case a methylene group in the 4 position is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined,

an imidazolyl group optionally substituted by 1 to 3 methyl groups,

a C_{5-7}-cycloalkyl group wherein a methylene group is replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, wherein R_{10} is as hereinbefore defined, or

F and G together denote a hydrogen, fluorine or chlorine atom,

a C_{1-6}-alkoxy group optionally substituted from position 2 onwards by a hydroxy or C_{1-4}-alkoxy group,

a C_{1-6}-alkoxy group which is substituted by an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group, while R_6 to R_9 are as hereinbefore defined,

a C_{3-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group, an amino group optionally substituted by 1 or 2 C_{1-4}-alkyl groups,

a 5- to 7-membered alkyleneimino group, wherein in the above-mentioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, or by a sulphinyl or sulphonyl group, while R_{10} is as hereinbefore defined,

with the proviso that at least one of the groups E, G or F together with G contains an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group or

D together with E contains an R_gCO-O-(R_eCR_f)-O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group or

E or G contains an optionally substituted 2-oxo-morpholinyl group,

a morpholino or thiomorpholino group substituted in the 2 position or in the 2 and 6 position by a C_{1-4}-alkoxy group,

a di-(C_{1-4}-alkoxy)-methyl or tri-(C_{1-4}-alkoxy)-methyl group or

an optionally substituted 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl-group or

E contains an optionally substituted 2-oxo-thiomorpholino group or an optionally substituted 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl-group,

whilst by the aryl moieties mentioned in the definitions of the abovementioned groups is meant a phenyl group which may in each case be monosubstituted by R_{12}, mono, di or trisubstituted by R_{13} or monosubstituted by R_{12} and additionally mono or disubstituted by R_{13}, wherein the substituents may be identical or different and

R_{12} denotes a cyano, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, hydroxy, C_{1-4}-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, C_{1-4}-alkylcarbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylcarbonylamino, C_{1-4}-alkylsulphonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylsulphonylamino, aminosulphonyl, C_{1-4}-alkylaminosulphonyl or di-(C_{1-4}-alkyl)-aminosulphonyl group or a carbonyl group, which is substituted by a 5- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino-group, and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

and moreover by the heteroaryl groups mentioned in the definitions of the abovementioned groups is meant a 5-membered heteroaromatic group which contains an imino group, an oxygen or sulphur atom or an imino group, an oxygen or sulphur atom and one or two nitrogen atoms, or

a 6-membered heteroaromatic group, which contains one, two or three nitrogen atoms,

whilst the abovementioned 5-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups and the abovementioned 6-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups or by a fluorine, chlorine, bromine or iodine atom, or by a trifluoromethyl, hydroxy, methoxy or ethoxy group,

the tautomers, the stereoisomers and the salts thereof.

2. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, while

R_1 and R_2, which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a methyl, ethyl, hydroxy, methoxy, ethoxy, amino, cyano, vinyl or ethynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms or

R_1 together with R_2, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH, -CH=CH-NH or -CH=N-NH group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an imino group optionally substituted by a methyl or ethyl group,

B denotes a carbonyl group,

C denotes a 1,1- or 1,2-vinylene group which is substituted in each case by one or two methyl groups or may be substituted by a trifluoromethyl group,

an ethynylene group or

a 1,3-butadien-1,4-ylene group optionally substituted by a methyl or trifluoromethyl group,

D denotes an alkylene or -CO-alkylene group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms, while the linking of the -CO-alkylene group to the adjacent group C in each case must take place via the carbonyl group,

a -CO-O-alkylene or -CO-NR_4-alkylene- group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms, while the linking to the adjacent group C in each case must take place via the carbonyl group wherein

R_4 denotes a hydrogen atom or a methyl or ethyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group which may be substituted by an R_6O-CO group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted in each case by a hydroxy, C_{1-4}-alkoxy, di-(C_{1-4}-alkyl)amino, C_{1-6}-alkylcarbonylsulphenyl, C_{3-6}-cycloalkylcarbonylsulphenyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylcarbonylsulphenyl, arylcarbonylsulphenyl or aryl-C_{1-3}-alkylcarbonylsulphenyl group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted in each case by a C_{1-6}-alkylcarbonyloxy, C_{3-6}-cycloalkylcarbonyloxy, C_{3-6}-cycloalkyl-C_{1-3}-alkylcarbonyloxy, arylcarbonyloxy or aryl-C_{1-3}-alkylcarbonyloxy group,

a C_{3-6}-cycloalkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group which may be substituted by a hydroxy, C_{1-4}-alkoxy, or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, while in the abovementioned 6- to 7-membered alkyleneimino groups, in each case a methylene group in the 4 position may be replaced by an oxygen atom or by an N-(C_{1-2}-alkyl)-imino group,

a C_{4-6}-cycloalkyl group,

a C_{3-5}-alkenyl or C_{3-5}-alkynyl group, while the unsaturated moiety may not be linked to the oxygen atom,

a C_{3-6}-cycloalkyl-C_{1-4}-alkyl, aryl, aryl-C_{1-4}-alkyl or R_gCO-O-(R_eCR_f) group, wherein

R_e and R_f, which may be identical or different, in each case denote a hydrogen atom or a C_{1-4}-alkyl group and

R_g denotes a C_{1-4}-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-alkoxy or C_{5-6}-cycloalkoxy group,

and R_9 denotes a C_{1-4}-alkyl group,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl, ethyl, acetyl or methylsulfonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a morpholino or homomorpholino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings in each case are additionally

substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a morpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a di-(C_{1-4}-alkoxy)-methyl group, while R_5 is as hereinbefore defined,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl group, while R_5 is as hereinbefore defined,

a $R_{11}NR_5$ group wherein R_5 is as hereinbefore defined and

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl, 2-oxo-tetrahydropyran-5-yl, 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group optionally substituted by one or two methyl groups,

or D together with E denotes a hydrogen atom,

a methyl, trifluoromethyl, aryl, R_gCO-O-(R_eCR_f)-O-CO or (R_7O-PO-OR_8) group wherein R_e to R_g and R_7 and R_8 are as hereinbefore defined,

F denotes an -O-C_{1-4}-alkylene group, wherein the alkylene moiety is linked to the group G, or an oxygen atom, while this may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_5 to R_9 are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or

bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group and additionally at cyclic carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a morpholino or homomorpholino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovemen-

tioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a C_{1-4}-alkyl or R_6O-CO-C_{1-4}-alkyl group, while R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group F,

a morpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a di-(C_{1-4}-alkoxy)-methyl group, while R_5 is as hereinbefore defined,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl group, while R_5 is as hereinbefore defined,

a R_hNR_5 group wherein R_5 is as hereinbefore defined and R_h denotes a substituted 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally by one or two methyl groups, or

F and G together denote a hydrogen atom,

a C_{1-4}-alkoxy group optionally substituted from position 2 onwards by a hydroxy or C_{1-4}-alkoxy group,

a C_{1-4}-alkoxy group which is substituted by an R_6O-CO group, where R_6 is as hereinbefore defined, or

a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group

with the proviso that at least one of the groups E, G or F together with G contains an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9) group or

D together with E contains an R_gCO-O-(R_eCR_f)-O-CO or (R_7O-PO-OR_8) group or

E or G contains an optionally substituted 2-oxo-morpholinyl group,

a morpholino group substituted in the 2 position or in the 2 and 6 positions in each case by a C_{1-4}-alkoxy group,

a di-(C_{1-4}-alkoxy)-methyl group or

an optionally substituted 1,3-dioxolan-2-yl, 1,3-dioxan-2-yl, 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group or

E contains an optionally substituted 2-oxo-thiomorpholino group or an optionally substituted 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group,

while the aryl moieties mentioned in the definition of the abovementioned groups denote a phenyl group which may in each case be monosubstituted by R_{12}, mono- or disubstituted by R_{13} or monosubstituted by R_{12} and additionally mono- or disubstituted by R_{13}, wherein the substituents may be identical or different and

R_{12} denotes a cyano, C_{1-2}-alkoxycarbonyl, aminocarbonyl, C_{1-2}-alkylaminocarbonyl, di-(C_{1-2}-alkyl)-aminocarbonyl, C_{1-2}-alkylsulphenyl, C_{1-2}-alkylsulphinyl, C_{1-2}-alkylsulphonyl, hydroxy, nitro, amino, C_{1-2}-alkylamino or di-(C_{1-2}-alkyl)-amino group and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, the stereoisomers and the salts thereof.

3. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, while

R_1 and R_2, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom, or a methyl, trifluoromethyl, methoxy, ethynyl or cyano group,

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a methine group substituted by a cyano group, or a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,1- or 1,2-vinylene group,

an ethynylene group or

a 1,3-butadien-1,4-ylene group,

D denotes a C_{1-4}-alkylene group,

a -CO-NR_4-alkylene group wherein the alkylene moiety contains 2 to 4 carbon atoms, while the linking to the adjacent group C in each case must take place via the carbonyl group, wherein

R_4 denotes a hydrogen atom,

or, if D is bound to a carbon atom of the group E, it may also denote a bond

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group which may be substituted by an R_6O-CO group,

an ethyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted by a C_{1-4}-alkylcarbonylsulphenyl, arylcarbonylsulphenyl or arylmethylcarbonylsulphenyl group,

an ethyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted by a hydroxy, C_{1-4}-alkylcarbonyloxy, arylcarbonyloxy or arylmethylcarbonyloxy group,

a 2,2-dimethoxyethyl or 2,2-diethoxyethyl group,

a C_{3-6}-cycloalkyl or C_{3-6}-cycloalkyl-methyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group,

a cyclopentyl, cyclopentylmethyl, cyclohexyl or cyclohexylmethyl group,

an aryl, arylmethyl or R_9CO-O-(R_eCR_f) group, while

R_e denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_f denotes a hydrogen atom and

R_g denotes a C_{1-4}-alkyl, cyclopentyl, cyclohexyl, C_{1-4}-alkoxy, cyclopentyloxy or cyclohexyloxy group,

and R_9 denotes a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-2}-alkyl groups wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl, ethyl, acetyl or methylsulfonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-2}-alkyl group and is additionally substituted at a cyclic carbon atom by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group wherein R_6 is as hereinbefore defined,

a morpholino group which is substituted by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_6 is as hereinbefore defined,

a piperidinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 or 2 C_{1-2}-alkyl groups,

a morpholino group which is substituted in the 2 position by a methoxy or ethoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a methoxy or ethoxy group,

a 2,2-dimethoxyethyl-NR_5, 2,2-diethoxyethyl-NR_5, 1,3-dioxolan-2-yl-methyl-NR_5 or 1,3-dioxan-2-yl-methyl-NR_5 group wherein R_5 is as hereinbefore defined,

a N-methyl-$R_{11}N$ or N-ethyl-$R_{11}N$ group wherein

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl, 2-oxo-tetrahydropyran-5-yl, 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group optionally substituted by one or two methyl groups,

or D together with E denotes a hydrogen atom,

a methyl, trifluoromethyl, aryl, $R_gCO-O-(R_eCR_f)-O-CO$ or $(R_7O-PO-OR_8)$ group wherein R_e to R_g and R_7 and R_8 are as hereinbefore defined,

F denotes an $-O-C_{1-4}$-alkylene group, while the alkylene moiety is linked to the group G, or an oxygen atom, which may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$-alkyl group, while R_5 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or $R_6O-CO-C_{1-2}$-alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or $R_6O-CO-C_{1-2}$-alkyl groups wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO, or $R_6O-CO-C_{1-2}$-alkyl group, while R_6 and R_{10} are as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-4}$-alkyl, bis-$(R_6O-CO)-C_{1-4}$-alkyl or $(R_7O-PO-OR_8)-C_{1-2}$-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-2}$-alkyl group and additionally at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-2}$-alkyl group wherein R_6 is as hereinbefore defined,

a morpholino group which is substituted by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_6 is as hereinbefore defined,

a piperidinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or R_6O-CO-C_{1-2}-alkyl group, while R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are each linked to a carbon atom of the group F,

a morpholino group which is substituted in the 2 position by a methoxy or ethoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a methoxy or ethoxy group,

a 2,2-dimethoxyethyl-NR_5, 2,2-diethoxyethyl-NR_5, 1,3-dioxolan-2-yl-methyl-NR_5 or 1,3-dioxan-2-yl-methyl-NR_5- group or

F and G together denote a hydrogen atom,

a methoxy or ethoxy group,

a C_{1-3}-alkoxy group which is substituted by an R_6O-CO group, while R_6 is as hereinbefore defined,

a C_{4-6}-cycloalkoxy or C_{3-6}-cycloalkyl-C_{1-3}-alkoxy group

with the proviso that at least one of the groups E, G or F together with G contains an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9) group or

D together with E contains an R_9CO-O-(R_eCR_f)-O-CO or (R_7O-PO-OR_8) group or

E or G contains an optionally substituted 2-oxo-morpholinyl group,

a morpholino group substituted in the 2 position or in the 2 and 6 positions in each case by a methoxy or ethoxy group,

a dimethoxymethyl or diethoxymethyl group or

an optionally substituted 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl- group or

E contains an optionally substituted 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl, 2-oxo-tetrahydropyran-5-yl, 2-oxo-thiomorpholino, 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group,

while the aryl moieties mentioned in the definition of the abovementioned groups denote a phenyl group which may be mono- or disubstituted by R_{13}, while the substituents may be identical or different and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-4}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, the stereoisomers and the salts thereof.

4. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3, wherein

R_1 and R_2, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom or a methyl group and

R_3 denotes a hydrogen atom,

R_c and R_d each denote a hydrogen atom,

X denotes a methine group substituted by a cyano group, or a nitrogen atom,

A denotes an imino group,

B denotes a carbonyl group,

C denotes a 1,2-vinylene or an ethynylene group,

D denotes a C_{1-4}-alkylene group,

a -CO-NR_4-alkylene group wherein the alkylene moiety contains 2 or 3 carbon atoms, while the linking to the adjacent group C must take place via the carbonyl group wherein

R_4 denotes a hydrogen atom,

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl group,

E denotes an R_6O-CO-alkylene-NR_5 or (R_7O-PO-OR_8)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 2 carbon atoms, may additionally be substituted by a methyl group or by an R_6O-CO or R_6O-CO-methyl group, while

R_5 denotes a hydrogen atom,

a C_{1-2}-alkyl group which may be substituted by an R_6O-CO group,

an ethyl group optionally substituted by one or two methyl groups, which is terminally substituted by a hydroxy, C_{1-2}-alkylcarbonylsulphenyl or C_{1-2}-alkylcarbonyloxy group,

a 2,2-dimethoxyethyl or 2,2-diethoxyethyl group,

R_6 denotes a hydrogen atom,

a C_{1-8}-alkyl group,

a cyclopentyl, cyclopentylmethyl, cyclohexyl or cyclohexylmethyl group,

a phenyl group optionally substituted by one or two methyl groups, a phenylmethyl group which may be substituted in the phenyl moiety by one or two methyl groups, a 5-indanyl group or an R_gCO-O-(R_eCR_f) group, while

R_e denotes a hydrogen atom or a methyl group,

R_f denotes a hydrogen atom and

R_g denotes a C_{1-4}-alkyl or C_{1-2}-alkoxy group,

R_7 and R_8, which may be identical or different, each denote a hydrogen atom, a methyl, ethyl or phenyl group,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or R_6O-CO-methyl group, wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or R_6O-CO-methyl groups wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO group, while R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl, ethyl, acetyl or methylsulfonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-methyl group and additionally at a cyclic carbon atom by an R_6O-CO group wherein R_6 is as hereinbefore defined,

a morpholino group which is substituted by an R_6O-CO- group, while R_6 is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 2 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 to 2 C_{1-2}-alkyl groups,

a morpholino group which is substituted in the 2 position by a methoxy or ethoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a methoxy or ethoxy group,

a 2,2-dimethoxyethyl-NR_5, 2,2-diethoxyethyl-NR_5 or 1,3-dioxolan-2-yl-methyl-NR_5- group wherein R_5 is as hereinbefore defined,

an N-methyl-$R_{11}N$ or N-ethyl-$R_{11}N$ group wherein

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

or D together with E denotes a hydrogen atom,

a methyl group or an R_gCO-O-(R_eCR_f)-O-CO group wherein R_e to R_g are as hereinbefore defined,

F denotes a -O-C_{1-4}-alkylene group, while the alkylene moiety is linked to the group G, or an oxygen atom, which may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by a methyl group or by an R_6O-CO or R_6O-CO-methyl group, while R_5 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or R_6O-CO-methyl group wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or R_6O-CO-methyl groups wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a piperidinyl group substituted in the 1 position by an R_6O-CO-C_{1-2}-alkyl group wherein R_6 is as hereinbefore defined, or

F and G together denote a hydrogen atom,

a methoxy or ethoxy group,

a C_{4-6}-cycloalkoxy or C_{3-6}-cycloalkyl-C_{1-3}-alkoxy group,

with the proviso that at least one of the groups E or G contains an R_6O-CO or (R_7O-PO-OR_8) group or

D together with E contains an R_9CO-O-(R_eCR_f)-O-CO group or

E contains an optionally substituted 2-oxo-morpholinyl group,

a morpholino group substituted in the 2 position or in the 2 and 6 positions in each case by a methoxy or ethoxy group,

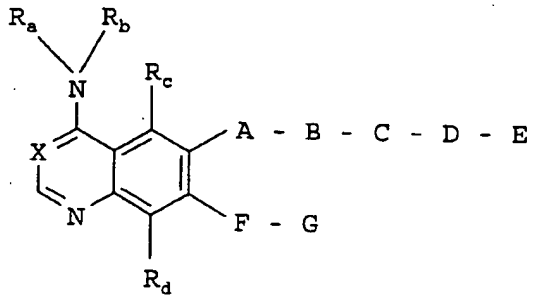
a dimethoxymethyl or diethoxymethyl group or

a 1,3-dioxolan-2-yl, 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group or

an optionally substituted 2-oxo-thiomorpholino group,

the tautomers, the stereoisomers and the salts thereof.

5. Bicyclic heterocycles of general formula



, (I)

wherein

R_a to R_d, A to C and X are defined as in claim 1,

D denotes an alkylene, -CO-alkylene or -SO_2-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms and additionally 1 to 4 hydrogen atoms in the alkylene moiety may be replaced by fluorine atoms, whilst the linking of the -CO-alkylene and -SO_2-alkylene group to the adjacent group C in each case must take place via the carbonyl or sulphonyl group,

a -CO-O-alkylene, -CO-NR_4-alkylene or -SO_2-NR_4-alkylene group wherein the alkylene moiety in each case contains 1 to 8 carbon atoms, whilst the linking to the adjacent group C in each case must take place via the carbonyl or sulphonyl group wherein

R_4 denotes a hydrogen atom or a C_{1-4}-alkyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5-group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon

atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group, which may be substituted by an R_6O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9) group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups, which may be terminally substituted in each case by a C_{1-6}-alkylcarbonylsulphenyl, C_{3-7}-cycloalkylcarbonylsulphenyl, C_{3-7}-cycloalkyl-C_{1-3}-alkylcarbonylsulphenyl, arylcarbonylsulphenyl or aryl-C_{1-3}-alkylcarbonylsulphenyl group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups which may be terminally substituted in each case by a C_{1-6}-alkylcarbonyloxy, C_{3-7}-cycloalkylcarbonyloxy, C_{3-7}-cycloalkyl-C_{1-3}-alkylcarbonyloxy, arylcarbonyloxy or aryl-C_{1-3}-alkylcarbonyloxy group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups, each of which may be terminally substituted by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-C_{1-3}-alkyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group, which may be substituted by a hydroxy, C_{1-4}-alkoxy, amino, C_{1-4}-alkylamino or di-(C_{1-4}-alkyl)-amino

group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group,

a C_{4-7}-cycloalkyl group optionally substituted by 1 or 2 methyl groups,

a C_{3-5}-alkenyl or C_{3-5}-alkynyl group, wherein the unsaturated part may not be linked to the oxygen atom,

a C_{3-7}-cycloalkyl-C_{1-4}-alkyl, aryl, aryl-C_{1-4}-alkyl or R_gCO-O-(R_eCR_f)-group, whilst

R_e and R_f, which may be identical or different, in each case denote a hydrogen atom or a C_{1-4}-alkyl group and

R_g denotes a C_{1-4}-alkyl, C_{3-7}-cycloalkyl, C_{1-4}-alkoxy or C_{5-7}-cycloalkoxy group,

and R_9 denotes a C_{1-4}-alkyl, aryl or aryl-C_{1-4}-alkyl group,

a 4- to 7-membered alkyleneimino group which may be substituted by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6OCO or R_6OCO-C_{1-4}-alkyl groups or by an R_6OCO-group and an R_6OCO-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl

or $(R_7O\text{-}PO\text{-}R_9)\text{-}C_{1\text{-}4}$-alkyl group wherein R_6 to R_9 are as hereinbefore defined and

R_{10} denotes a hydrogen atom, a $C_{1\text{-}4}$-alkyl, formyl, $C_{1\text{-}4}$-alkylcarbonyl or $C_{1\text{-}4}$-alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at cyclic carbon atoms by two $R_6O\text{-}CO$ or $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl groups or by an $R_6O\text{-}CO$-group and an $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl, bis-$(R_6O\text{-}CO)\text{-}C_{1\text{-}4}$-alkyl, $(R_7O\text{-}PO\text{-}OR_8)\text{-}C_{1\text{-}4}$-alkyl or $(R_7O\text{-}PO\text{-}R_9)\text{-}C_{1\text{-}4}$-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl, bis-$(R_6O\text{-}CO)\text{-}C_{1\text{-}4}$-alkyl, $(R_7O\text{-}PO\text{-}OR_8)\text{-}C_{1\text{-}4}$-alkyl or $(R_7O\text{-}PO\text{-}R_9)\text{-}C_{1\text{-}4}$-alkyl group and is additionally substituted at cyclic carbon atoms by one or two $R_6O\text{-}CO$ or $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl groups or by an $R_6O\text{-}CO$-group and an $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted in each case by an $R_6O\text{-}CO$, $(R_7O\text{-}PO\text{-}OR_8)$, $(R_7O\text{-}PO\text{-}R_9)$, $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl, bis-$(R_6O\text{-}CO)\text{-}C_{1\text{-}4}$-alkyl, $(R_7O\text{-}PO\text{-}OR_8)\text{-}C_{1\text{-}4}$-alkyl or $(R_7O\text{-}PO\text{-}R_9)\text{-}C_{1\text{-}4}$-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted by two $R_6O\text{-}CO$ or $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl groups or by an $R_6O\text{-}CO$-group and an $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, whilst the abovemen-

tioned 5- to 7-membered rings are additionally substituted in each case at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a morpholino or thiomorpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino or thiomorpholino group which is substituted in the 2 and 6 positions by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5-group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is in each case terminally substituted by a di-(C_{1-4}-alkoxy)-methyl or tri-(C_{1-4}-alkoxy)-methyl group, whilst R_5 is as hereinbefore defined,

a C_{1-4}-alkyl-NR_5-group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is in each case terminally substituted by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl group optionally substituted by one or two methyl groups, while R_5 is as hereinbefore defined,

an $R_{11}NR_5$-group wherein R_5 is as hereinbefore defined and

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl, 2-oxo-tetrahydropyran-5-yl, 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group optionally substituted by one or two methyl groups,

or D together with E denotes an R_gCO-O-(R_eCR_f)-O-CO, (R_7O-PO-OR_8) or (R_7O-PO-R_9)-group wherein R_e to R_g and R_7 to R_9 are as hereinbefore defined,

F and G together denote a hydrogen atom,
a C_{1-6}-alkoxy group optionally substituted from position 2 onwards by a hydroxy or C_{1-4}-alkoxy group,

a C_{3-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group,

whilst by the aryl moieties mentioned in the definitions of the abovementioned groups is meant a phenyl group which in

each case may be monosubstituted by R_{12}, mono-, di- or trisubstituted by R_{13} or monosubstituted by R_{12} and additionally mono- or disubstituted by R_{13}, whilst the substituents may be identical or different and

R_{12} denotes a cyano, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, hydroxy, C_{1-4}-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, C_{1-4}-alkylcarbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylcarbonylamino, C_{1-4}-alkylsulphonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylsulphonylamino, aminosulphonyl, C_{1-4}-alkylaminosulphonyl or di-(C_{1-4}-alkyl)-aminosulphonyl group or a carbonyl group, which is substituted by a 5- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino-group, and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, the stereoisomers and the salts thereof.

6. Bicyclic heterocycles of general formula I according to claim 5, wherein
R_a to R_d, A to C and X are defined as in claim 2,

D denotes an alkylene or -CO-alkylene group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms, while the linking of the -CO-alkylene group to the adjacent group C in each case must take place via the carbonyl group,

a -CO-O-alkylene or -CO-NR_4-alkylene- group wherein the alkylene moiety in each case contains 1 to 4 carbon atoms, while the linking to the adjacent group C in each case must take place via the carbonyl group wherein

R_4 denotes a hydrogen atom or a methyl or ethyl group,

or, if D is bound to a carbon atom of the group E, it may also denote a bond

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl or sulphonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group which may be substituted by an R_6O-CO group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted in each case by a hydroxy, C_{1-4}-alkoxy, di-(C_{1-4}-alkyl)amino, C_{1-6}-alkylcarbonylsulphenyl, C_{3-6}-cycloalkylcarbonylsulphenyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylcarbonylsulphenyl, arylcarbonylsulphenyl or aryl-C_{1-3}-alkylcarbonylsulphenyl group,

an ethyl or propyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted in each case by a C_{1-6}-alkylcarbonyloxy, C_{3-6}-cycloalkylcarbonyloxy, C_{3-6}-cycloalkyl-C_{1-3}-alkylcarbonyloxy, arylcarbonyloxy or aryl-C_{1-3}-alkylcarbonyloxy group,

a C_{3-6}-cycloalkyl or C_{3-6}-cycloalkyl-C_{1-3}-alkyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group which may be substituted by a hydroxy, C_{1-4}-alkoxy, or di-(C_{1-4}-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, while in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen atom or by an N-(C_{1-2}-alkyl)-imino group,

a C_{4-6}-cycloalkyl group,

a C_{3-5}-alkenyl or C_{3-5}-alkynyl group, while the unsaturated moiety may not be linked to the oxygen atom,

a C_{3-6}-cycloalkyl-C_{1-4}-alkyl, aryl, aryl-C_{1-4}-alkyl or R_gCO-O-(R_eCR_f) group, while

R_e and R_f, which may be identical or different, in each case denote a hydrogen atom or a C_{1-4}-alkyl group and

R_g denotes a C_{1-4}-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-alkoxy or C_{5-6}-cycloalkoxy group,

and R_9 denotes a C_{1-4}-alkyl group,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl, ethyl, acetyl or methylsulfonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl, or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is as hereinbefore defined,

a morpholino or homomorpholino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or

bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 to 4 C_{1-2}-alkyl groups,

a morpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a di-(C_{1-4}-alkoxy)-methyl group, while R_5 is as hereinbefore defined,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl group, while R_5 is as hereinbefore defined,

a $R_{11}NR_5$ group wherein R_5 is as hereinbefore defined and

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl, 2-oxo-tetrahydropyran-5-yl, 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group optionally substituted by one or two methyl groups,

or D together with E denotes an R_gCO-O-(R_eCR_f)-O-CO or $(R_7O$-PO-$OR_8)$ group wherein R_e to R_g and R_7 to R_9 are as hereinbefore defined,

F and G together denote a hydrogen atom,

a C_{1-6}-alkoxy group optionally substituted from position 2 by a hydroxy or C_{1-4}-alkoxy group,

a C_{4-7}-cycloalkoxy or C_{3-7}-cycloalkyl-C_{1-4}-alkoxy group,

whilst by the aryl moieties mentioned in the definitions of the abovementioned groups is meant a phenyl group which in each case may be monosubstituted by R_{12}, mono- or disubstituted by R_{13} or monosubstituted by R_{12} and additionally mono- or disubstituted by R_{13}, whilst the substituents may be identical or different and

R_{12} denotes a cyano, C_{1-2}-alkoxycarbonyl, aminocarbonyl, C_{1-2}-alkylaminocarbonyl, di-$(C_{1-2}$-alkyl)-aminocarbonyl, C_{1-2}-alkylsulphenyl, C_{1-2}-alkylsulphinyl, C_{1-2}-alkylsulphonyl, hy-

droxy, nitro, amino, C_{1-2}-alkylamino or di-(C_{1-2}-alkyl)-amino, and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, the stereoisomers and the salts thereof.

7. Bicyclic heterocycles of general formula I according to claim 5, wherein

R_a to R_d, A to C and X are defined as in claim 3,

D denotes a C_{1-4}-alkylene group,

a -CO-NR_4-alkylene group wherein the alkylene moiety contains 2 to 4 carbon atoms, while the linking to the adjacent group C in each case must take place via the carbonyl group, wherein

R_4 denotes a hydrogen atom,

or, if D is bound to a carbon atom of the group E, it may also denote a bond

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl group,

E denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while

R_5 denotes a hydrogen atom,

a C_{1-4}-alkyl group which may be substituted by an R_6O-CO group,

an ethyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted by a C_{1-4}-alkylcarbonylsulphenyl, arylcarbonylsulphenyl or arylmethylcarbonylsulphenyl group,

an ethyl group optionally substituted by one or two methyl or ethyl groups which is terminally substituted by a hydroxy, C_{1-4}-alkylcarbonyloxy, arylcarbonyloxy or arylmethylcarbonyloxy group,

a 2,2-dimethoxyethyl or 2,2-diethoxyethyl group,

a C_{3-6}-cycloalkyl or C_{3-6}-cycloalkyl-methyl group,

R_6, R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom,

a C_{1-8}-alkyl group,

a cyclopentyl, cyclopentylmethyl, cyclohexyl or cyclohexylmethyl group,

an aryl, arylmethyl or R_gCO-O-(R_eCR_f) group, wherein

R_e denotes a hydrogen atom or a C_{1-4}-alkyl group,

R_f denotes a hydrogen atom and

R_g denotes a C_{1-4}-alkyl, cyclopentyl, cyclohexyl, C_{1-4}-alkoxy, cyclopentyloxy or cyclohexyloxy group,

and R_9 denotes a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-2}-alkyl groups wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl, ethyl, acetyl or methylsulfonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-2}-alkyl group and is additionally substituted at a cyclic carbon atom by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group wherein R_6 is as hereinbefore defined,

a morpholino group which is substituted by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_6 is as hereinbefore defined,

a piperidinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 2 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 to 2 C_{1-2}-alkyl groups,

a morpholino group which is substituted in the 2 position by a methoxy or ethoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a methoxy or ethoxy group,

a 2,2-dimethoxyethyl-NR_5, 2,2-diethoxyethyl-NR_5, 1,3-dioxolan-2-yl-methyl-NR_5 or 1,3-dioxan-2-yl-methyl-NR_5 group wherein R_5 is as hereinbefore defined,

a N-methyl-$R_{11}N$ or N-ethyl-$R_{11}N$ group wherein

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl, 2-oxo-tetrahydropyran-5-yl, 2-oxo-tetrahydrothiophen-3-yl, 2-oxo-tetrahydrothiophen-4-yl, 2-oxo-tetrahydrothiopyran-3-yl, 2-oxo-tetrahydrothiopyran-4-yl or 2-oxo-tetrahydrothiopyran-5-yl group optionally substituted by one or two methyl groups,

or D together with E denotes an R_gCO-O-(R_eCR_f)-O-CO or (R_7O-PO-OR_8) group wherein R_e to R_g and R_7 and R_8 are as hereinbefore defined,

F and G together denote a hydrogen atom, a methoxy, ethoxy, C_{4-6}-cycloalkoxy or C_{3-6}-cycloalkyl-C_{1-3}-alkoxy group,

while the aryl moieties mentioned in the definition of the abovementioned groups denote a phenyl group which may be mono- or disubstituted by R_{13}, while the substituents may be identical or different and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-4}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, the stereoisomers and the salts thereof.

8. Bicyclic heterocycles of general formula I according to claim 5, wherein

R_a to R_d, A to C and X are defined as in claim 4,

D denotes a C_{1-4}-alkylene group,

a -CO-NR_4-alkylene group wherein the alkylene moiety contains 2 or 3 carbon atoms, while the linking to the adjacent group C must take place via the carbonyl group wherein

R_4 denotes a hydrogen atom,

or, if D is bound to a nitrogen atom of the group E, it may also denote a carbonyl group,

E denotes an R_6O-CO-alkylene-NR_5 or (R_7O-PO-OR_8)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 2 carbon atoms, may additionally be substituted by a methyl group or by an R_6O-CO or R_6O-CO-methyl group, while

R_5 denotes a hydrogen atom,

a C_{1-2}-alkyl group which may be substituted by an R_6O-CO group,

an ethyl group optionally substituted by one or two methyl groups, which is terminally substituted by a hydroxy, C_{1-2}-alkylcarbonylsulphenyl or C_{1-2}-alkylcarbonyloxy group,

a 2,2-dimethoxyethyl or 2,2-diethoxyethyl group,

R_6 denotes a hydrogen atom,

a C_{1-8}-alkyl group,

a cyclopentyl, cyclopentylmethyl, cyclohexyl or cyclohexylmethyl group,

a phenyl group optionally substituted by one or two methyl groups, a phenylmethyl group which may be substituted in the phenyl moiety by one or two methyl groups, a 5-indanyl group or an R_gCO-O-(R_eCR_f) group, while

R_e denotes a hydrogen atom or a methyl group,

R_f denotes a hydrogen atom and

R_g denotes a C_{1-4}-alkyl or C_{1-2}-alkoxy group,

R_7 and R_8, which may be identical or different, in each case denote a hydrogen atom, a methyl, ethyl or phenyl group,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or R_6O-CO-methyl group, wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or R_6O-CO-methyl groups wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO group, while R_6 is as hereinbefore defined and

R_{10} denotes a hydrogen atom, a methyl, ethyl, acetyl or methylsulfonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an R_6O-CO-methyl group and additionally at a cyclic carbon atom by an R_6O-CO group wherein R_6 is as hereinbefore defined,

a morpholino group which is substituted by an R_6O-CO- group, wherein R_6 is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 2 C_{1-2}-alkyl groups,

a 2-oxo-thiomorpholino group which may be substituted by 1 to 2 C_{1-2}-alkyl groups,

a morpholino group which is substituted in the 2 position by a methoxy or ethoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a methoxy or ethoxy group,

a 2,2-dimethoxyethyl-NR_5, 2,2-diethoxyethyl-NR_5 or 1,3-dioxolan-2-yl-methyl-NR_5- group wherein R_5 is as hereinbefore defined,

an N-methyl-$R_{11}N$ or N-ethyl-$R_{11}N$ group wherein

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

or D together with E denotes an $R_gCO-O-(R_eCR_f)-O-CO$ group wherein R_e to R_g are as hereinbefore defined,

F and G together denote a hydrogen atom,

a methoxy, ethoxy, C_{4-6}-cycloalkoxy or C_{3-6}-cycloalkyl-C_{1-3}-alkoxy group,

the tautomers, the stereoisomers and the salts thereof.

9. Bicyclic heterocycles of general formula I according to at least one of claims 5 to 8, characterised in that R_b denotes one of the optionally substituted 1-phenyl-ethyl groups mentioned in the respective claim 5, 6, 7 or 8,

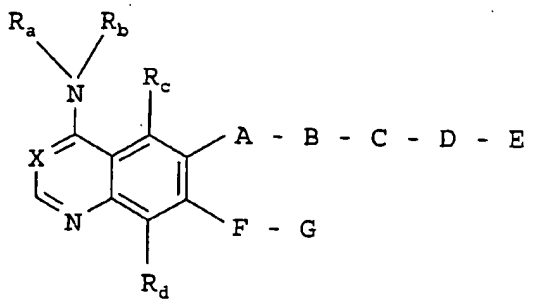
the tautomers, the stereoisomers and the salts thereof.

10. Bicyclic heterocycles of general formula I according to at least one of claims 5 to 8, characterised in that F and G together denote one of the cycloalkoxy or cycloalkyl-alkoxy groups mentioned in the respective claim 5, 6, 7 or 8,

the tautomers, the stereoisomers and the salts thereof.

11. Bicyclic heterocycles of general formula I according to at least one of claims 5 to 8, characterised in that E denotes one of the optionally substituted 2-oxo-morpholino groups mentioned in the respective claim 5, 6, 7 or 8.

12. Bicyclic heterocycles of general formula



, (I)

wherein

R_a to R_d, A to C and X are defined as in claim 1,

D together with E denotes a hydrogen atom,

a C_{1-4}-alkyl group optionally substituted by 1 to 5 fluorine atoms,

a C_{3-6}-cycloalkyl group,

an aryl, heteroaryl, C_{1-4}-alkylcarbonyl, arylcarbonyl or C_{1-4}-alkoxycarbonyl group,

an aminocarbonyl, C_{1-4}-alkylaminocarbonyl or di-(C_{1-4}-alkyl)-aminocarbonyl group or

a carbonyl group, which is substituted by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups, a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by an imino group substituted by the group R_{10}, by a sulphinyl or sulphonyl group, wherein R_{10} is defined as in claim 1,

F denotes a C_{1-6}-alkylene group, a -O-C_{1-6}-alkylene group, wherein the alkylene moiety is linked to the group G, or an oxygen atom, whilst the latter may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5-group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, wherein R_5 to R_9 are defined as in claim 1,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are defined as in claim 1,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 is defined as in claim 1,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are defined as in claim 1,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 and R_{10} are defined as in claim 1,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are defined as in claim 1,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group and is

additionally substituted at cyclic carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 to R_9 are defined as in claim 1,

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are defined as in claim 1,

a morpholino or homomorpholino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 is defined as in claim 1,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at a carbon atom by an R_6O-CO, (R_7O-PO-OR_8), (R_7O-PO-R_9), R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_{10} are defined as in claim 1,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups or by an R_6O-CO-group and an R_6O-CO-C_{1-4}-alkyl group wherein R_6 and R_{10} are defined as in claim 1,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are defined as in claim 1,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-

C_{1-4}-alkyl, $(R_7O\text{-}PO\text{-}OR_8)\text{-}C_{1-4}$-alkyl or $(R_7O\text{-}PO\text{-}R_9)\text{-}C_{1-4}$-alkyl group, while the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two $R_6O\text{-}CO$ or $R_6O\text{-}CO\text{-}C_{1-4}$-alkyl groups or by an $R_6O\text{-}CO$-group and an $R_6O\text{-}CO\text{-}C_{1-4}$-alkyl group wherein R_6 to R_9 are defined as in claim 1,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4}-alkyl, $R_6O\text{-}CO\text{-}C_{1-4}$-alkyl, $(R_7O\text{-}PO\text{-}OR_8)\text{-}C_{1-4}$-alkyl or $(R_7O\text{-}PO\text{-}R_9)\text{-}C_{1-4}$-alkyl group, while R_6 to R_9 are defined as in claim 1 and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group F,

a morpholino or thiomorpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino or thiomorpholino group which is substituted in the 2 and 6 position by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5-group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is in each case terminally substituted by a di-(C_{1-4}-alkoxy)-methyl or tri-(C_{1-4}-alkoxy)-methyl group, whilst R_5 is defined as in claim 1,

a C_{1-4}-alkyl-NR_5-group wherein the C_{1-4}-alkyl moiety, which is straight-chained and may additionally be substituted by one or two methyl groups, is terminally substituted in each case by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl-group optionally substituted by one or two methyl groups, while R_5 is defined as in claim 1,

an R_hNR_5-group wherein R_5 is as hereinbefore defined and R_h denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two methyl groups,

whilst by the aryl moieties mentioned in the definitions of the abovementioned groups is meant a phenyl group which in each case may be monosubstituted by R_{12}, mono-, di- or tri-substituted by R_{13} or monosubstituted by R_{12} and additionally mono- or disubstituted by R_{13}, whilst the substituents may be identical or different and

R_{12} denotes a cyano, carboxy, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-4}-alkylaminocarbonyl, di-(C_{1-4}-alkyl)-aminocarbonyl, C_{1-4}-alkylsulphenyl, C_{1-4}-alkylsulphinyl, C_{1-4}-alkylsulphonyl, hydroxy, C_{1-4}-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4}-alkylamino, di-(C_{1-4}-alkyl)-amino, C_{1-4}-alkylcarbonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylcarbonylamino, C_{1-4}-alkylsulphonylamino, N-(C_{1-4}-alkyl)-C_{1-4}-alkylsulphonylamino, aminosulphonyl, C_{1-4}-alkylaminosulphonyl or di-(C_{1-4}-alkyl)-aminosulphonyl group or a carbonyl group, which is substituted by a 5- to 7-membered alkyleneimino group, wherein in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-4}-alkyl)-imino group, and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4}-alkyl, trifluoromethyl or C_{1-4}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

and moreover, the heteroaryl groups mentioned in the definitions of the abovementioned groups also include a 5-membered

heteroaromatic group which contains an imino group, an oxygen or sulphur atom or an imino group, an oxygen or sulphur atom and one or two nitrogen atoms, or

a 6-membered heteroaromatic group which contains one, two or three nitrogen atoms,

whilst the abovementioned 5-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups and the abovementioned 6-membered heteroaromatic groups may be substituted in each case by 1 or 2 methyl or ethyl groups or by a fluorine, chlorine, bromine or iodine atom, or by a trifluoromethyl, hydroxy, methoxy or ethoxy group,

the tautomers, the stereoisomers and the salts thereof.

13. Bicyclic heterocycles of general formula I according to claim 12, wherein

R_a to R_d, A to C and X are defined as in claim 2,

D together with E denotes a hydrogen atom,

a methyl, trifluoromethyl or aryl group,

F denotes an -O-C_{1-4}-alkylene group, wherein the alkylene moiety is linked to the group G, or an oxygen atom, while this may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5, (R_7O-PO-OR_8)-alkylene-NR_5 or (R_7O-PO-R_9)-alkylene-NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_5 to R_9 are defined as in claim 2,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is defined as in claim 2,

a 4- to 7-membered alkyleneimino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is defined as in claim 2,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at a cyclic carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 and R_{10} are defined as in claim 2,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are defined as in claim 2,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are defined as in claim 2,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group and additionally at cyclic carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is defined as in claim 2,

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 is defined as in claim 2,

a morpholino or homomorpholino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is defined as in claim 2,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6O-CO, R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group wherein R_6 and R_{10} are defined as in claim 2,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10}, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 and R_{10} are defined as in claim 2,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl, (R_7O-PO-OR_8)-C_{1-4}-alkyl or (R_7O-PO-R_9)-C_{1-4}-alkyl group wherein R_6 to R_9 are defined as in claim 2,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl or bis-(R_6O-CO)-C_{1-4}-alkyl group, while the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by one or two R_6O-CO or R_6O-CO-C_{1-4}-alkyl groups wherein R_6 is defined as in claim 2,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a C_{1-4}-alkyl or R_6O-CO-C_{1-4}-alkyl group, while R_6 is defined as in claim 2 and the abovementioned 2-oxo-morpholinyl groups are each are linked to a carbon atom of the group F,

a morpholino group which is substituted in the 2 position by a C_{1-4}-alkoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a C_{1-4}-alkoxy group,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a di-(C_{1-4}-alkoxy)-methyl group, while R_5 is defined as in claim 2,

a C_{1-4}-alkyl-NR_5 group wherein the C_{1-4}-alkyl moiety, which is straight-chained, is terminally substituted by a 1,3-dioxolan-2-yl or 1,3-dioxan-2-yl group, while R_5 is defined as in claim 2,

a R_hNR_5 group wherein R_5 is defined as in claim 2 and R_h denotes a substituted 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally by one or two methyl groups,

while the aryl moieties mentioned in the definition of the abovementioned groups denote a phenyl group which may in each case be monosubstituted by R_{12}, mono- or disubstituted by R_{13} or monosubstituted by R_{12} and additionally mono or disubstituted by R_{13}, while the substituents may be identical or different and

R_{12} denotes a cyano, C_{1-2}-alkoxycarbonyl, aminocarbonyl, C_{1-2}-alkylaminocarbonyl, di-(C_{1-2}-alkyl)-aminocarbonyl, C_{1-2}-alkylsulphenyl, C_{1-2}-alkylsulphinyl, C_{1-2}-alkylsulphonyl, hydroxy, nitro, amino, C_{1-2}-alkylamino or di-(C_{1-2}-alkyl)-amino group and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-5}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, the stereoisomers and the salts thereof.

14. Bicyclic heterocycles of general formula I according to claim 12, wherein

R_a to R_d, A to C and X are defined as in claim 3,

D together with E denotes a hydrogen atom,

a methyl, trifluoromethyl or aryl group,

F denotes an -O-C_{1-4}-alkylene group, wherein the alkylene moiety is linked to the group G, or an oxygen atom, while this may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C_{1-2}-alkyl groups or by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_5 and R_6 are defined as in claim 3,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group wherein R_6 is defined as in claim 3,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or R_6O-CO-C_{1-2}-alkyl groups wherein R_6 is defined as in claim 3,

a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO, or R_6O-CO-C_{1-2}-alkyl group, while R_6 and R_{10} are defined as in claim 3,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are defined as in claim 3,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-2}-alkyl group and additionally at a cyclic carbon atom by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group wherein R_6 is defined as in claim 3,

a morpholino group which is substituted by an R_6O-CO or R_6O-CO-C_{1-2}-alkyl group, while R_6 is defined as in claim 3,

a piperidinyl group substituted in the 1 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are defined as in claim 3,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or R_6O-CO-C_{1-2}-alkyl group, while R_6 is defined as in claim 3 and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group F,

a morpholino group which is substituted in the 2 position by a methoxy or ethoxy group,

a morpholino group which is substituted in the 2 and 6 positions in each case by a methoxy or ethoxy group,

a 2,2-dimethoxyethyl-NR_5, 2,2-diethoxyethyl-NR_5, 1,3-dioxolan-2-yl-methyl-NR_5 or 1,3-dioxan-2-yl-methyl-NR_5 group wherein R_5 is defined as in claim 3,

while the aryl moieties mentioned in the definition of the abovementioned groups denote a phenyl group which may be mono- or disubstituted by R_{13}, while the substituents may be identical or different and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-2}-alkyl, trifluoromethyl or C_{1-2}-alkoxy group or

two groups R_{13}, if they are bound to adjacent carbon atoms, together denote a C_{3-4}-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, the stereoisomers and the salts thereof.

15. Bicyclic heterocycles of general formula I according to claim 12, wherein

R_a to R_d, A to C and X are defined as in claim 4,

D together with E denotes a hydrogen atom or a methyl group,

F denotes an -O-C_{1-4}-alkylene group, while the alkylene moiety is linked to the group G, or an oxygen atom, which may not be linked to a nitrogen atom of the group G, and

G denotes an R_6O-CO-alkylene-NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by a methyl group or by an R_6O-CO or R_6O-CO-methyl group, while R_5 and R_6 are defined as in claim 4,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or R_6O-CO-methyl group wherein R_6 is defined as in claim 4,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or R_6O-CO-methyl groups wherein R_6 is defined as in claim 4,

a piperazino group which is substituted in the 4 position by an R_6O-CO-C_{1-4}-alkyl, bis-(R_6O-CO)-C_{1-4}-alkyl or (R_7O-PO-OR_8)-C_{1-2}-alkyl group wherein R_6 to R_8 are defined as in claim 4,

a piperidinyl group substituted in the 1 position by an R_6O-CO-C_{1-2}-alkyl group wherein R_6 is defined as in claim 4,

the tautomers, the stereoisomers and the salts thereof.

16. Bicyclic heterocycles of general formula I according to at least one of claims 12 to 15, characterised in that R_b denotes one of the optionally substituted 1-phenyl-ethyl groups mentioned in the respective claim 12, 13, 14 or 15,

the tautomers, the stereoisomers and the salts thereof.

17. The following compounds of general formula I according to claim 1:

(a) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline,

(b) 4-[(3-bromophenyl)amino]-7-(3-{4-[3-(ethoxycarbonyl)propyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline,

(c) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}oxy)-6-[(vinylcarbonyl)amino]-quinazoline,

(d) 4-[(3-bromophenyl)amino]-7-(3-{4-[(diethoxyphosphoryl)-methyl]-piperazin-1-yl}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline,

(e) 4-[(3-bromophenyl)amino]-7-(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyloxy)-6-[(vinylcarbonyl)amino]-quinazoline,

(f) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-quinazoline,

(g) 4-[(3-bromophenyl)amino]-6-[(4-{N-[(diethoxyphosphoryl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline,

(h) (*R*)-4-[(1-phenylethyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-7-methoxy-quinazoline,

(i) 4-[(3-bromophenyl)amino]-6-({4-[N-(2,2-dimethoxyethyl)-N-methylamino]-1-oxo-2-buten-1-yl}amino)-7-methoxy-quinazoline,

(j) 4-[(3-bromophenyl)amino]-6-{[4-(2-ethoxy-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline,

(k) 4-[(3-bromophenyl)amino]-3-cyano-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}-1-oxo-2-buten-1-yl)amino]-quinoline,

(l) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

(m) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

(n) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline,

(o) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-cyclobutyloxy-quinazoline,

(p) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-1-oxo-2-buten-1-yl)amino]-7-(2-cyclopropylethoxy)-quinazoline,

(q) (*S*)-4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[2-(methoxycarbonyl)-pyrrolidin-1-yl]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline,

(r) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)methyl]-N-[2-(acetylsulphanyl)ethyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

(s) 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[(ethoxycarbonyl)-methyl]-N-[2-(methylcarbonyloxy)ethyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

(t) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclo-propylmethoxy-quinazoline and

(u) 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(5-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline

and the salts thereof.

18. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 17 with inorganic or organic acids or bases.

19. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 17 or a physiologically accep-

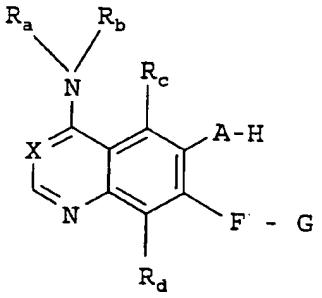
table salt according to claim 18 optionally together with one or more inert carriers and/or diluents.

20. Use of a compound according to at least one of claims 1 to 18 for preparing a pharmaceutical composition which is suitable for treating benign or malignant tumours, for preventing and treating diseases of the airways and lungs and for treating polyps, diseases of the gastrointestinal tract, the bile duct and gall bladder and also the kidneys and skin.

21. Process for preparing a pharmaceutical composition according to claim 19, characterised in that a compound according to at least one of claims 1 to 18 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

22. Process for preparing the compounds of general formula I according to claims 1 to 18, characterised in that

a) a compound of general formula



, (II)

wherein

R_a to R_d, A, F, G and X are defined as in claims 1 to 17, is reacted with a compound of general formula

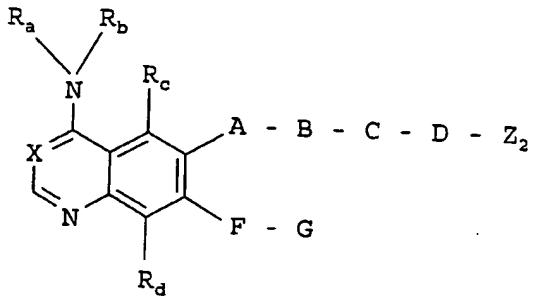
$$Z_1 - B - C - D - E \qquad , (III)$$

wherein

B to E are defined as in claims 1 to 17 and

Z_1 denotes a leaving group or a hydroxy group, or

b) in order to prepare compounds of general formula I wherein the group E is linked to the group D via a nitrogen atom, a compound of general formula



, (IV)

wherein

R_a to R_d, A to D, F, G and X are defined as in claims 1 to 17 and

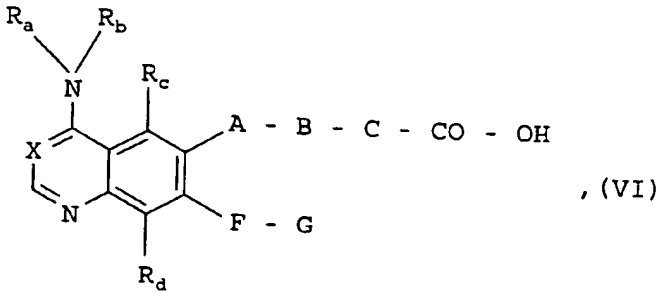
Z_2 denotes a leaving group or a hydroxy group, is reacted with a compound of general formula

, (V)

wherein

Y denotes one of the groups mentioned for E in claims 1 to 17, which is linked to the group D via a nitrogen atom, or

c) for preparing compounds of general formula I wherein D together with E denotes an $R_gCO\text{-}O\text{-}(R_eCR_f)\text{-}O\text{-}CO$- group, a compound of general formula



, (VI)

wherein
R_a to R_d, A to C, F, G and X are defined as in claims 1 to 17, is reacted with a compound of general formula

$$R_gCO\text{-}O\text{-}(R_eCR_f)\text{-}Z_3 \quad , (VII)$$

wherein
R_e to R_g are defined as in claims 1 to 17 and
Z_3 denotes a leaving group or

d) for preparing compounds of general formula I wherein E or G denotes a piperazino or homopiperazino group each substituted in position 4 by an $R_6O\text{-}CO\text{-}C_{1\text{-}4}$-alkyl group wherein R_6 is defined as in claims 1 to 17, a corresponding compound containing a piperazino or homopiperazino group each unsubstituted in position 4 is reacted with a compound of general formula

$$R_6O\text{-}CO\text{-}C_{1\text{-}4}\text{-alkyl-}Z_4 \quad (VIII),$$

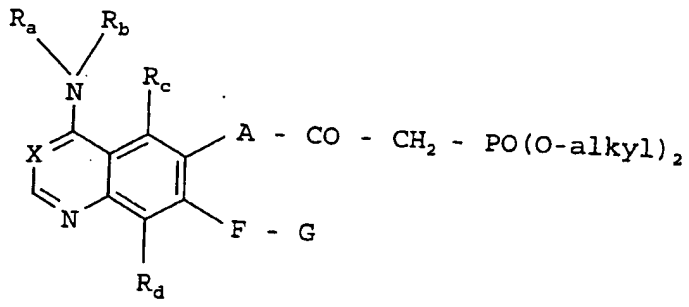
wherein
R_6 is defined as in claims 1 to 17 and
Z_4 denotes a leaving group, or

e) for preparing compounds of general formula I wherein E or G denotes a piperazino or homopiperazino group each substituted in position 4 by an $R_6O\text{-}CO\text{-}CH_2CH_2$-group wherein R_6 is defined as in claims 1 to 17, a corresponding compound containing a piperazino or homopiperazino group each unsubstituted in position 4 is reacted with a compound of general formula

$$R_6O\text{-}CO\text{-}CH{=}CH_2, \quad (IX),$$

wherein
R_6 is defined as in claims 1 to 17, or

f) for preparing compounds of general formula I wherein C denotes a 1,2-vinylene group, a compound of general formula



, (X)

wherein

R_a to R_d, A, F, G and X are defined as in claims 1 to 17 and alkyl denotes a lower alkyl group, is reacted with a compound of general formula

OCH-D-E (XI),

wherein

D and E are defined as in claims 1 to 17, and

if desired a compound of general formula I thus obtained which contains a hydroxy, amino, alkylamino or imino group is converted by acylation or sulphonylation into a corresponding acylamino, N-alkyl-acylamino, acyl-imino, sulphonyloxy, sulphonylamino, N-alkyl-sulphonylamino or sulphonyl-imino compound, whilst a sulphonyloxy compound thus obtained may be converted into a corresponding sulphenyl compound by reaction with an alkali metal salt of a thio compound, and/or

a compound of general formula I thus obtained which contains an amino, alkylamino or imino group is converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I, and/or

a compound of general formula I thus obtained wherein E denotes a bis-[2,2-di-(C_{1-4}-alkoxy)ethyl]amino group may be converted by intramolecular cyclisation into a corresponding morpholino compound of general formula I, and/or

a compound of general formula I thus obtained wherein E or G denotes an optionally substituted N-(2-hydroxyethyl)-glycine or N-(2-hydroxyethyl)-glycine ester group may be converted by intramolecular cyclisation into a corresponding 2-oxo-morpholino compound, and/or

a compound of general formula I thus obtained which contains a carboxy or hydroxyphosphoryl group may be converted by alkylation into a corresponding ester of general formula I, and/or

if necessary any protecting group used during the reactions described above is cleaved again and/or

if desired a compound of general formula I thus obtained is resolved into the stereoisomers thereof and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/EP 00/01496

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/94 C07D215/54 A61K31/517 A61K31/4706 A61P35/00
C07F9/40 C07D401/12 C07D493/12 C07D403/12 C07D405/12
C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 09016 A (AMERICAN CYANAMID CO) 25 February 1999 (1999-02-25) page 77 -page 82; claim 1	1-8, 12-15, 18-22
A	EP 0 787 722 A (AMERICAN CYANAMID CO) 6 August 1997 (1997-08-06) page 21 -page 22; claim 1 page 18; example 5	1-22
E	WO 00 18740 A (AMERICAN CYANAMID CO) 6 April 2000 (2000-04-06) page 120 -page 127; claim 1 page 106; example 105	1-8, 12-15, 18-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 June 2000	04/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
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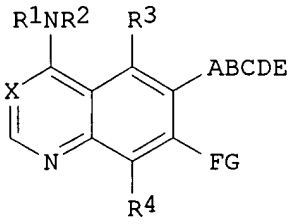
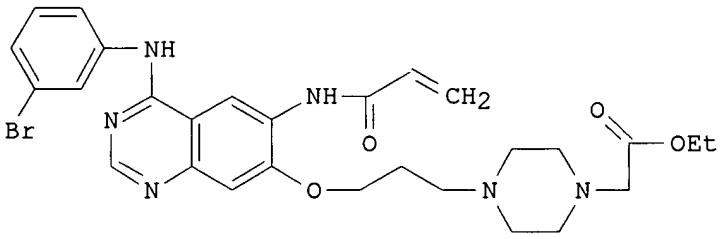
		US 5760041 A	02-06-1998
		ZA 9700913 A	04-08-1998
WO 0018740 A	06-04-2000	NONE	



I



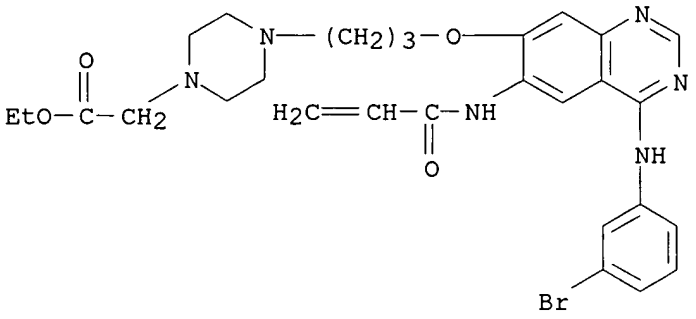
II

AB Title compds. [I; R1 = H, C1-C4-alkyl; R2 = (un)substituted Ph, benzyl, 1-phenylethyl; R3, R4 independently = H, F, Cl, CH3O, CH3OCH2, (CH3)2NCH2, (CH3CH2)2NCH2, pyrrolidino, piperidino, morpholino; X = C(CN), N; A = O, NH, (C1-C4)-alkylN; B = CO, SO2; C = 1,3-allenylene, 1,1-vinylene, 1,2-vinylene, 1,3-butadien-1,4-ylene, with CH3, CF3 substitution; D = alkylene, CO-alkylene, SO2-alkylene; CO, SO2; E = HOCO(CH2)nNR5, (HO)2P(:O)(CH2)nNR5; n = 1-6; R5 = H, alkyl], tautomers, stereoisomers, and physiol. acceptable salts are prepd. and having valuable pharmacol. properties, particularly an inhibiting effect on signal transduction mediated by tyrosine kinases. Title compds. are useful for treating tumoral diseases, diseases of the lungs and respiratory tract. Thus, the title compd. II was prepd. and tested by Cell Titer 96TM Aq. Nonradioactive Cell Proliferation Assay.

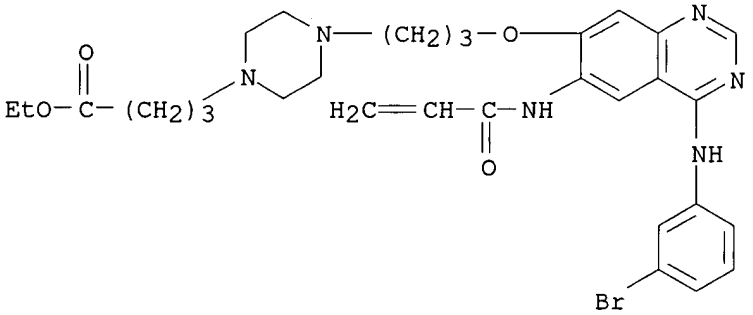
IT **289700-58-9P 289700-62-5P 289700-64-7P 290301-61-0P 290301-96-1P 290302-11-3P 290302-25-9P 290302-33-9P 290302-39-5P 290302-47-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)

RN 289700-58-9 CAPLUS

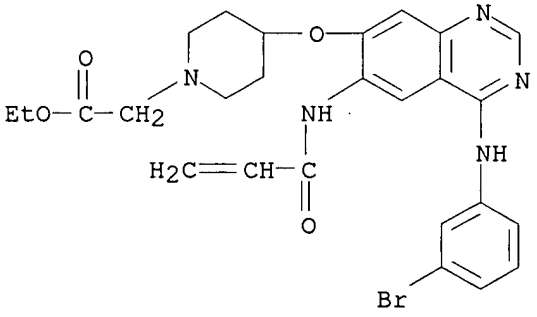
CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



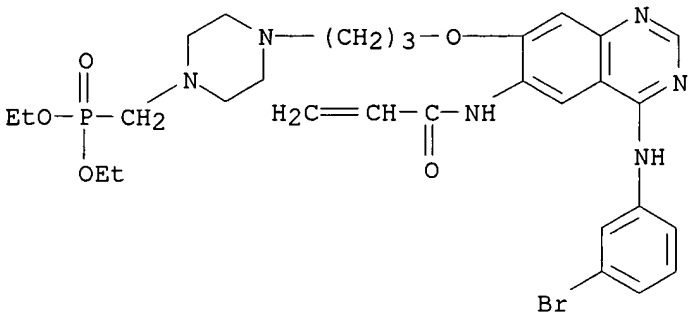
RN 289700-62-5 CAPLUS
CN 1-Piperazinebutanoic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



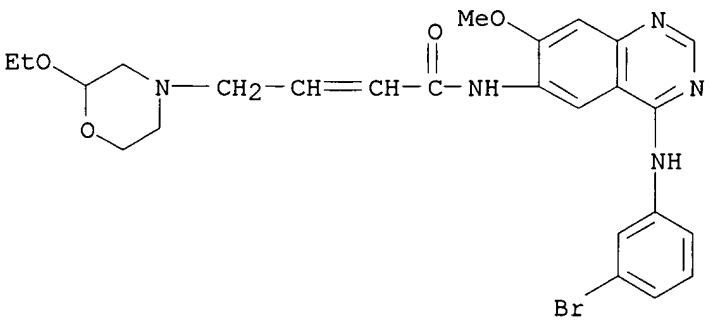
RN 289700-64-7 CAPLUS
CN 1-Piperidineacetic acid, 4-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)



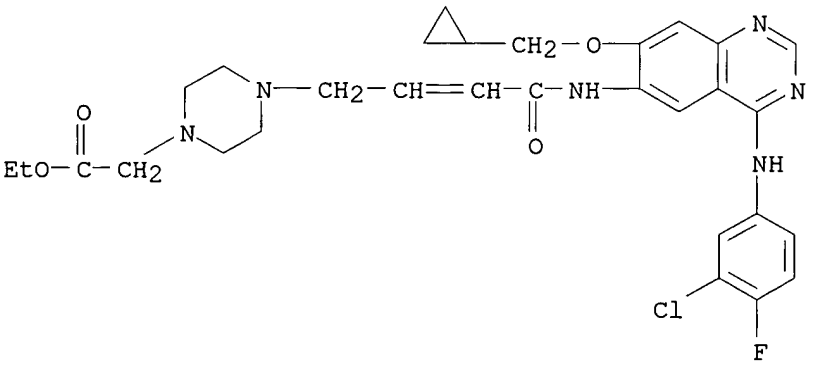
RN 290301-61-0 CAPLUS
CN Phosphonic acid, [[4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-1-piperazinyl]methyl]-, diethyl ester (9CI) (CA INDEX NAME)



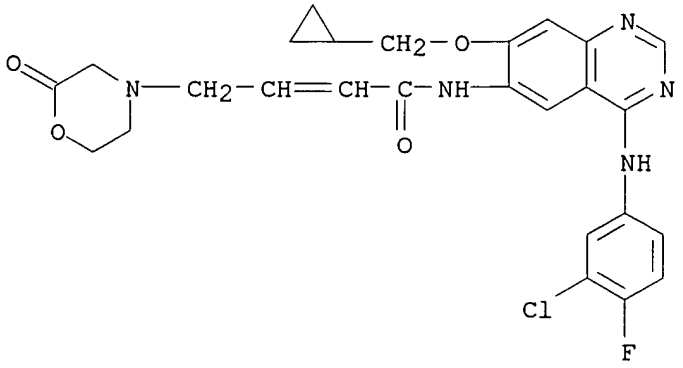
RN 290301-96-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-7-methoxy-6-quinazolinyl]-4-(2-ethoxy-4-morpholinyl)- (9CI) (CA INDEX NAME)



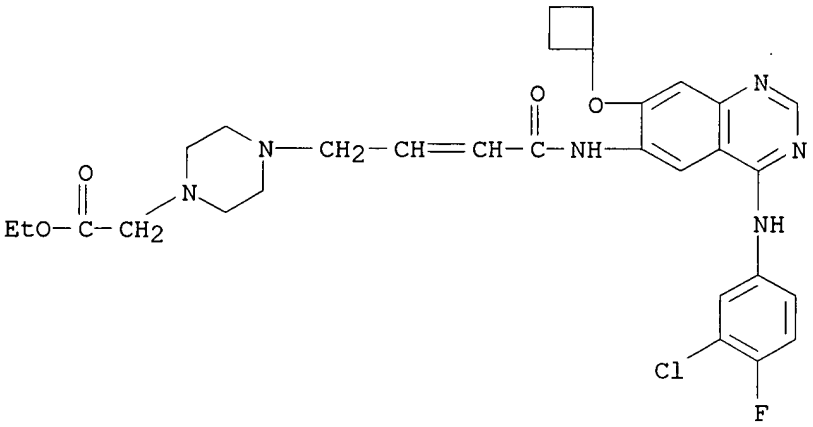
RN 290302-11-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



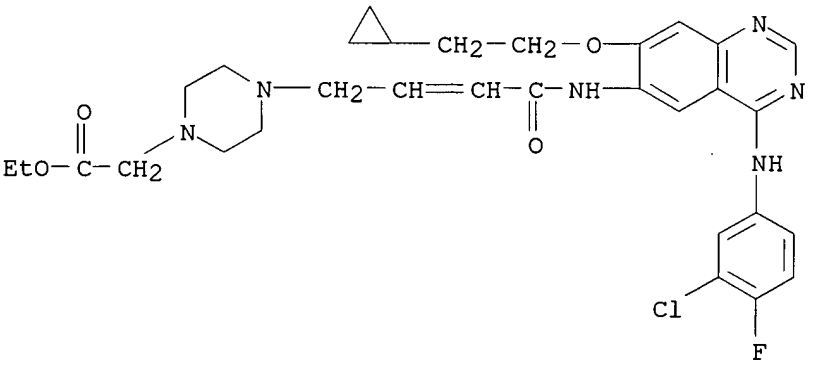
RN 290302-25-9 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)



RN 290302-33-9 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

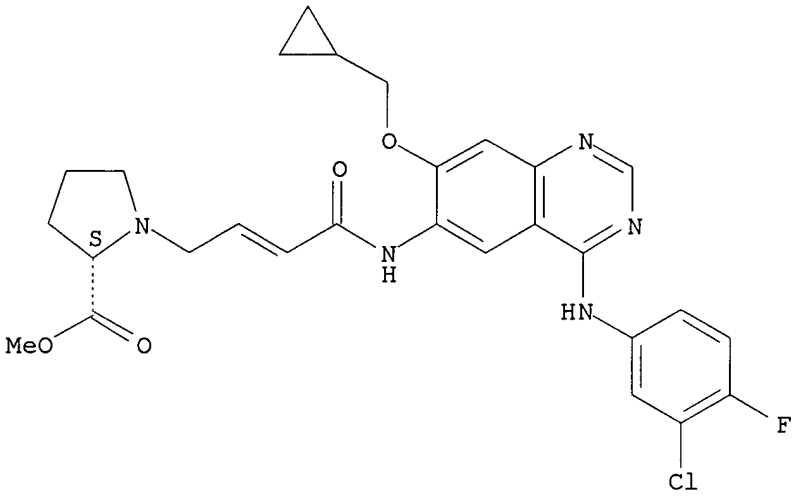


RN 290302-39-5 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(2-cyclopropylethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

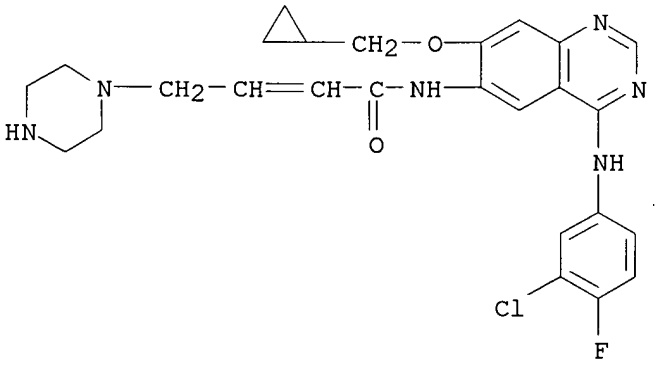


RN 290302-47-5 CAPLUS
CN L-Proline, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

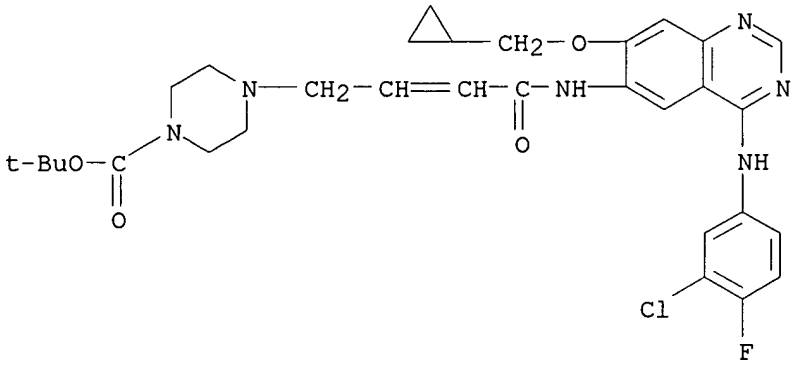


IT **290303-47-8P 290304-01-7P 290304-02-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)
RN 290303-47-8 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(1-piperazinyl)- (9CI) (CA INDEX NAME)

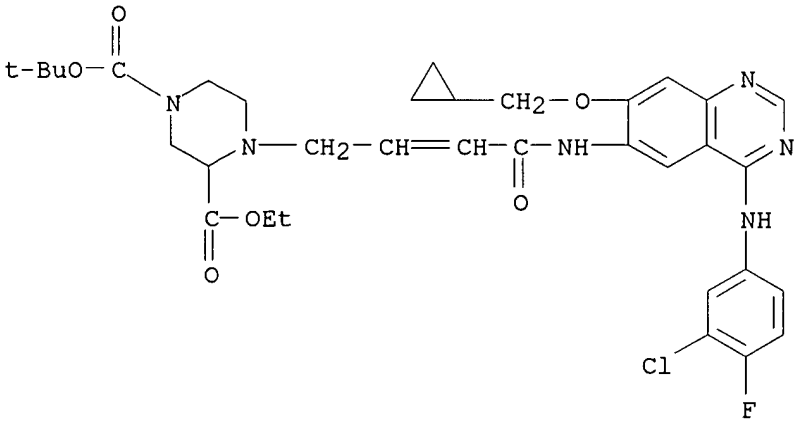


RN 290304-01-7 CAPLUS
CN 1-Piperazinecarboxylic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-,

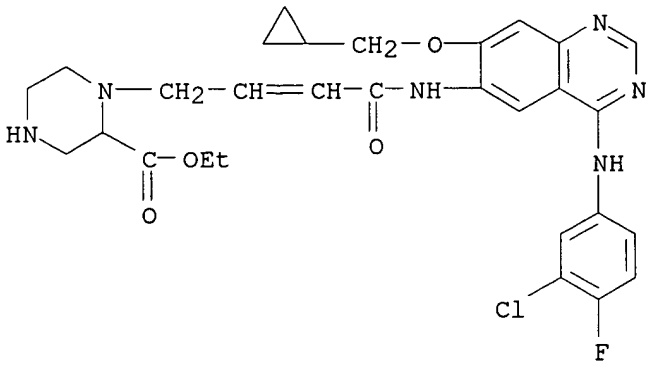
1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 290304-02-8 CAPLUS
CN 1,3-Piperazinedicarboxylic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1-(1,1-dimethylethyl) 3-ethyl ester (9CI) (CA INDEX NAME)



IT **290303-13-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)
RN 290303-13-8 CAPLUS
CN 2-Piperazinecarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



IT **289700-59-0P 289700-60-3P 289700-61-4P**
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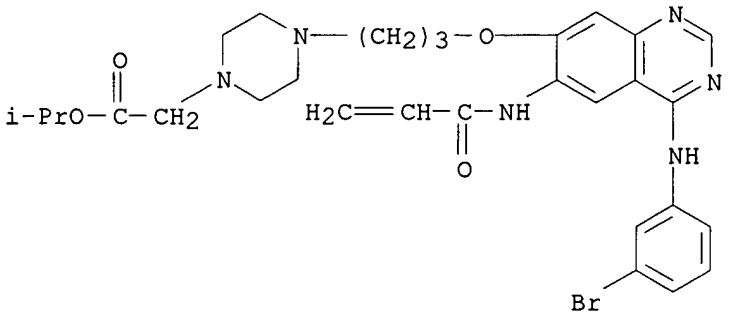
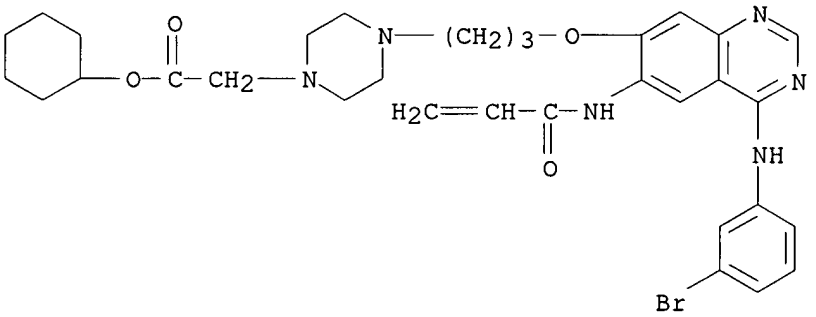
290303-12-7P 290303-14-9P 290303-15-0P
290303-16-1P 290303-17-2P 290303-18-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazoline and aminoquinoline derivs. having an inhibitory effect on signal transduction mediated by tyrosine kinases useful for treating tumoral diseases, lung and respiratory tract diseases)

RN 289700-59-0 CAPLUS

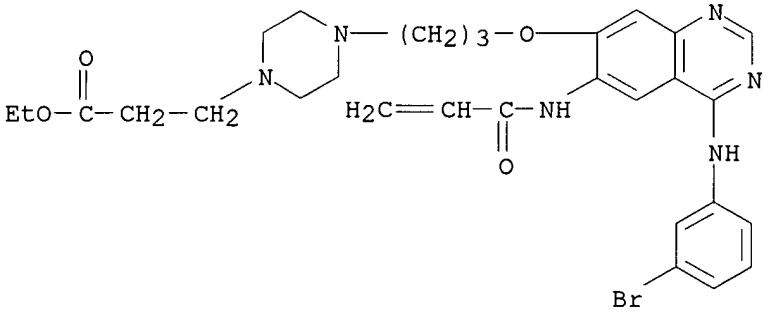
CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



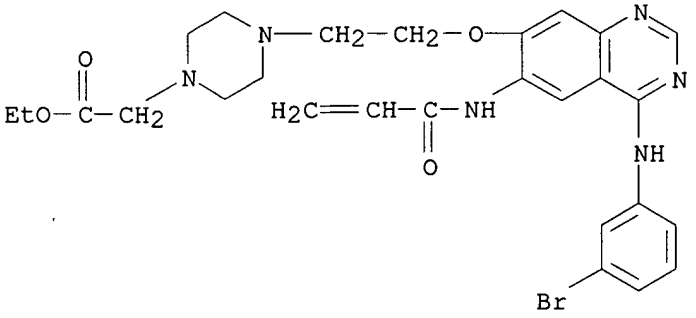
RN 289700-60-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, cyclohexyl ester (9CI) (CA INDEX NAME)



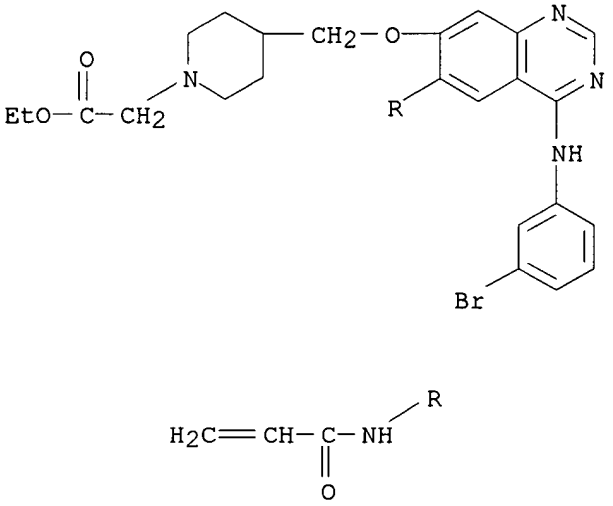
RN 289700-61-4 CAPLUS
CN 1-Piperazinepropanoic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



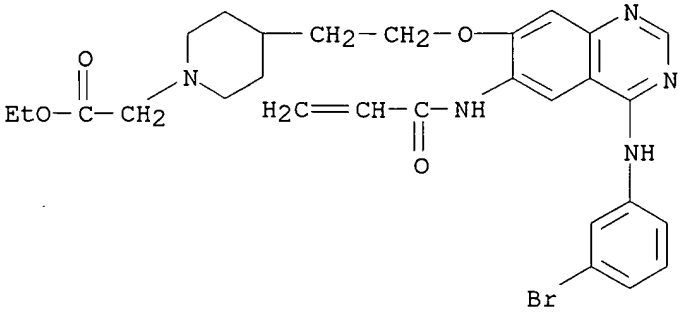
RN 289700-63-6 CAPLUS
CN 1-Piperazineacetic acid, 4-[2-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]ethyl]-, ethyl ester (9CI) (CA INDEX NAME)



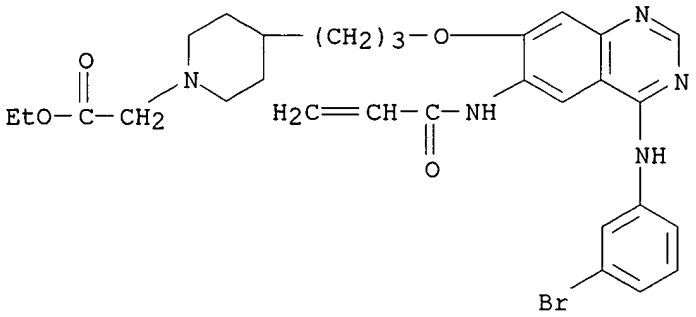
RN 289700-65-8 CAPLUS
CN 1-Piperidineacetic acid, 4-[[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]methyl]-, ethyl ester (9CI) (CA INDEX NAME)



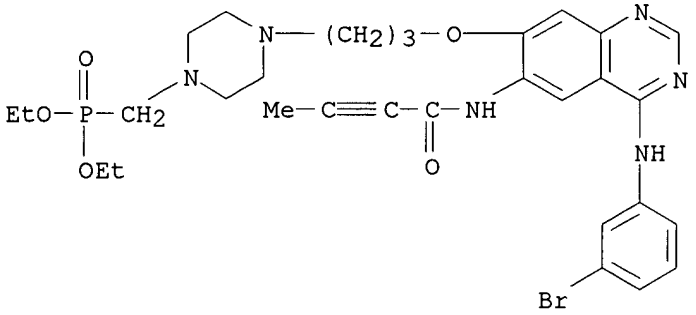
RN 289700-66-9 CAPLUS
CN 1-Piperidineacetic acid, 4-[2-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]ethyl]-, ethyl ester (9CI) (CA INDEX NAME)



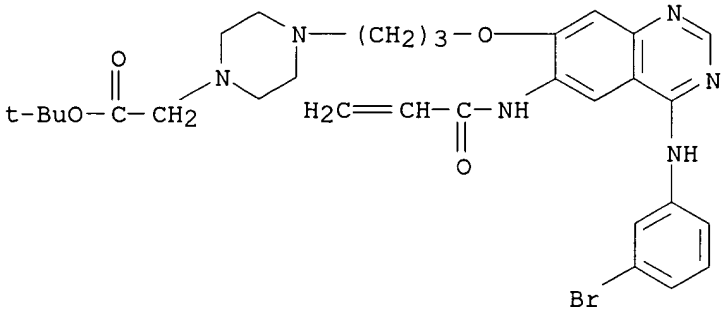
RN 289700-67-0 CAPLUS
CN 1-Piperidineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 290301-62-1 CAPLUS
CN Phosphonic acid, [[4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-butynyl)amino]-7-quinazolinyl]oxy]propyl]-1-piperazinyl]methyl]-, diethyl ester (9CI) (CA INDEX NAME)



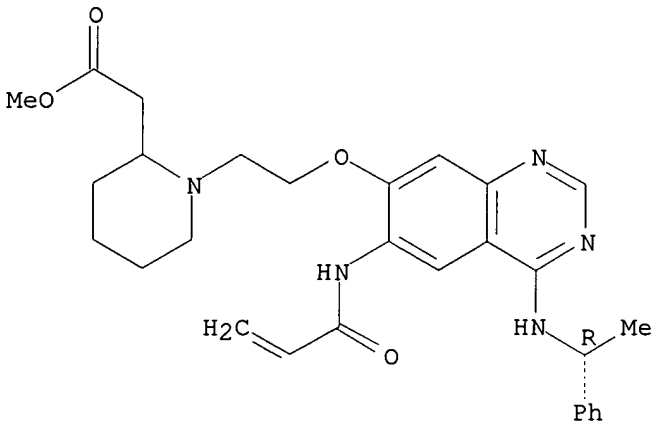
RN 290301-63-2 CAPLUS
CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



RN 290301-67-6 CAPLUS

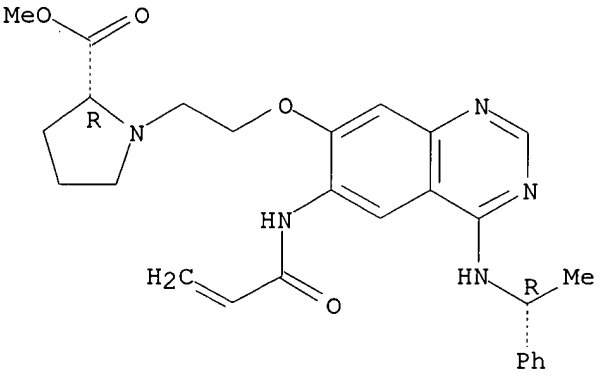
CN 2-Piperidineacetic acid, 1-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



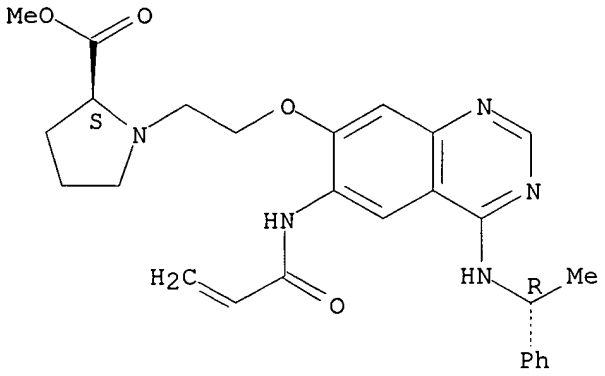
RN 290301-68-7 CAPLUS
CN D-Proline, 1-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



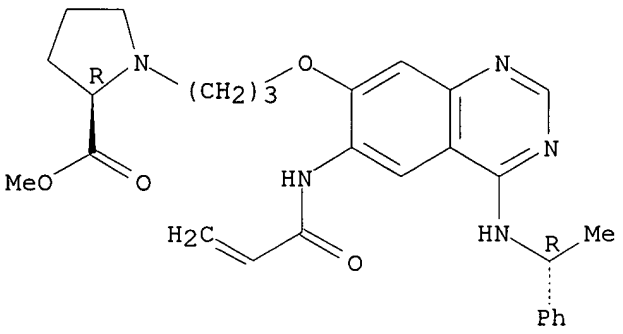
RN 290301-69-8 CAPLUS
CN L-Proline, 1-[2-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



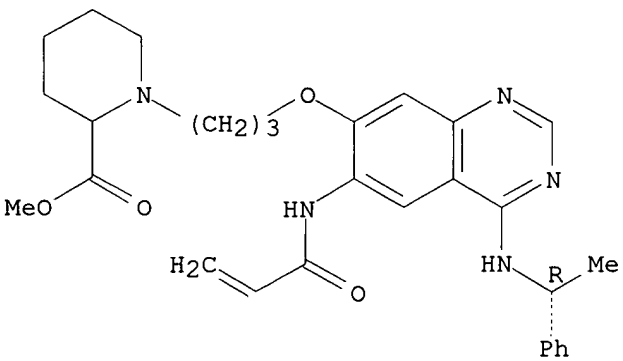
RN 290301-70-1 CAPLUS
CN D-Proline, 1-[3-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]propyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

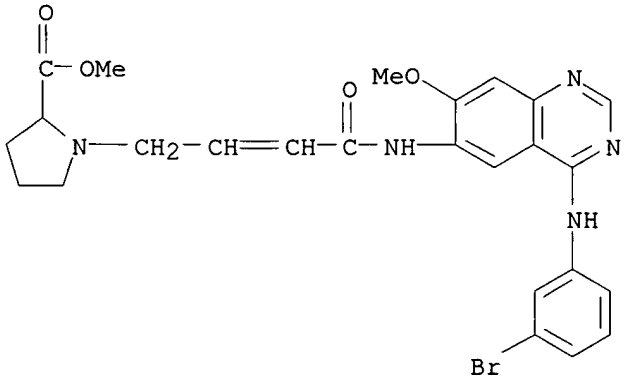


RN 290301-71-2 CAPLUS
CN 2-Piperidinecarboxylic acid, 1-[3-[[6-[(1-oxo-2-propenyl)amino]-4-[[(1R)-1-phenylethyl]amino]-7-quinazolinyl]oxy]propyl]-, methyl ester (9CI) (CA INDEX NAME)

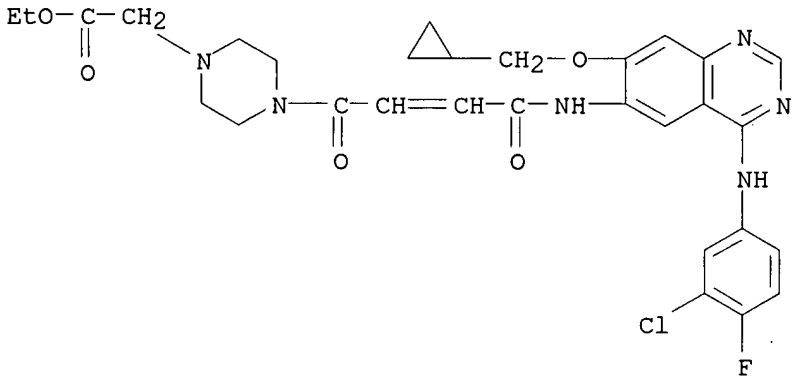
Absolute stereochemistry.



RN 290301-74-5 CAPLUS
CN Proline, 1-[4-[[4-[(3-bromophenyl)amino]-7-methoxy-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, methyl ester (9CI) (CA INDEX NAME)

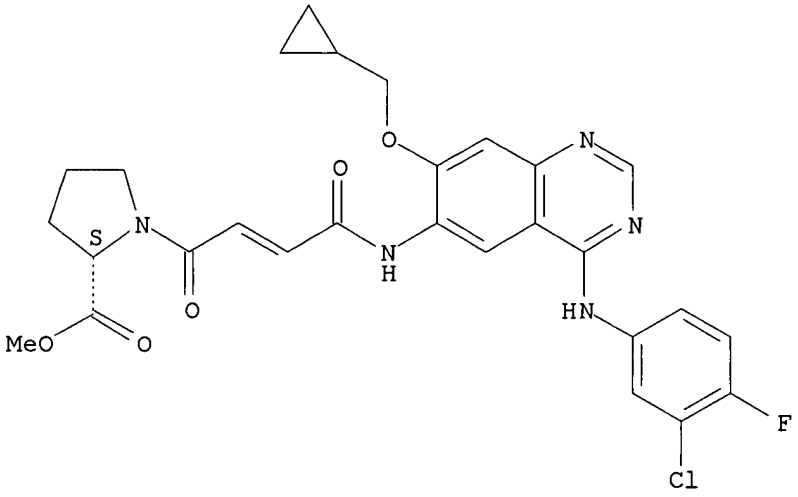


RN 290301-81-4 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-1,4-dioxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

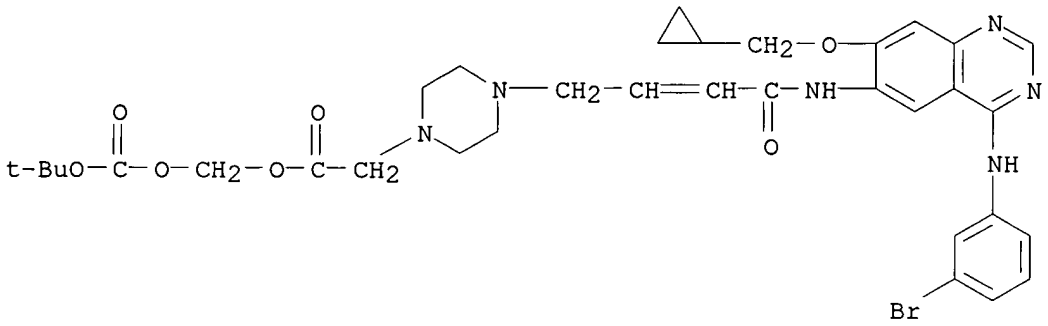


RN 290301-82-5 CAPLUS
CN L-Proline, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-1,4-dioxo-2-butenyl]-, methyl ester (9CI) (CA INDEX NAME)

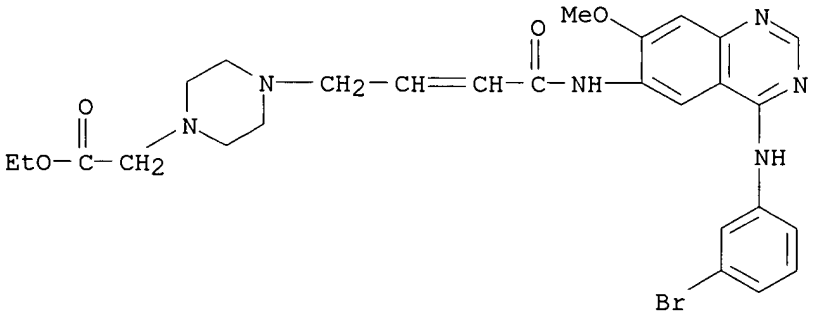
Absolute stereochemistry.
Double bond geometry unknown.



RN 290301-85-8 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-bromophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, [[(1,1-dimethylethoxy)carbonyl]oxy]methyl ester (9CI) (CA INDEX NAME)

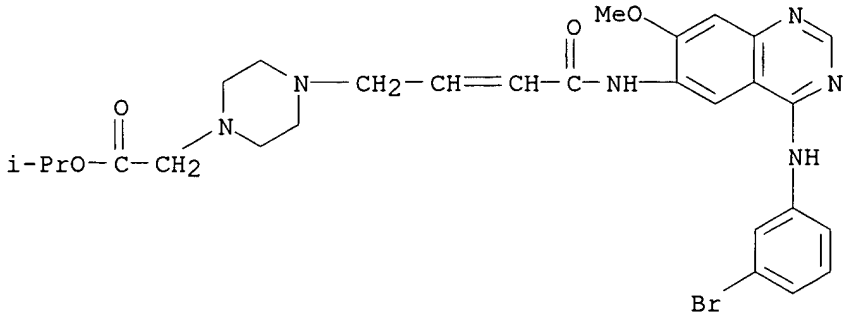


RN 290301-92-7 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-bromophenyl)amino]-7-methoxy-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

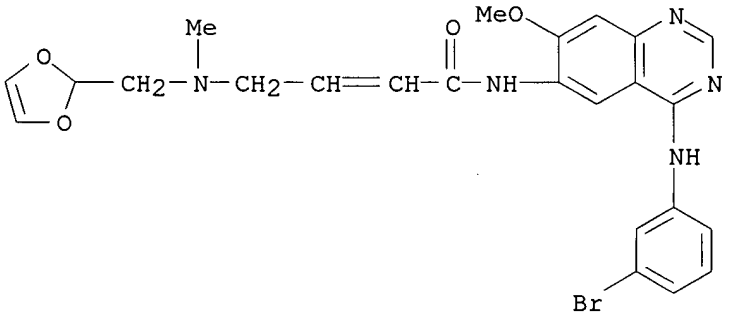


RN 290301-93-8 CAPLUS

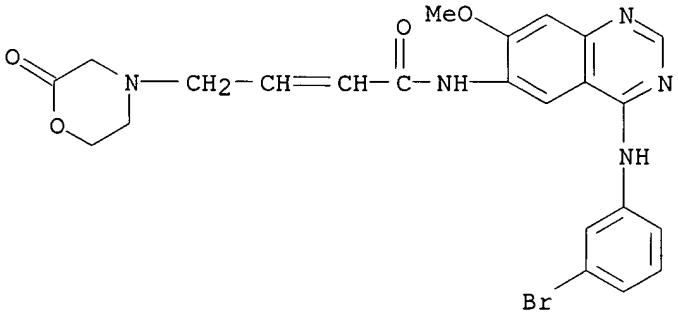
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-bromophenyl)amino]-7-methoxy-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



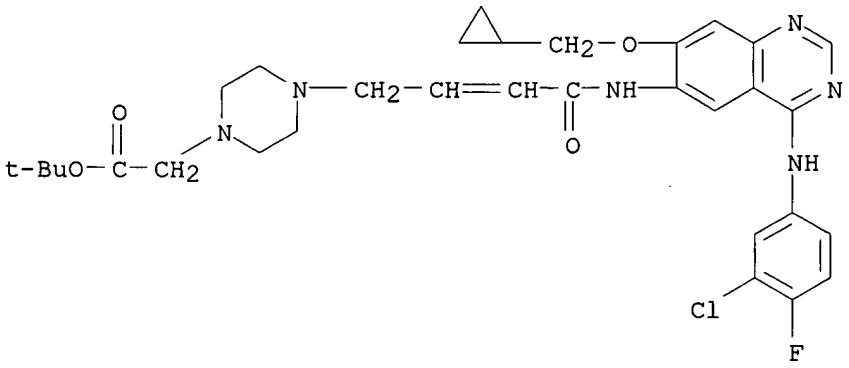
RN 290301-95-0 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-7-methoxy-6-quinazolinyl]-4-[(1,3-dioxol-2-ylmethyl)methylamino]- (9CI) (CA INDEX NAME)



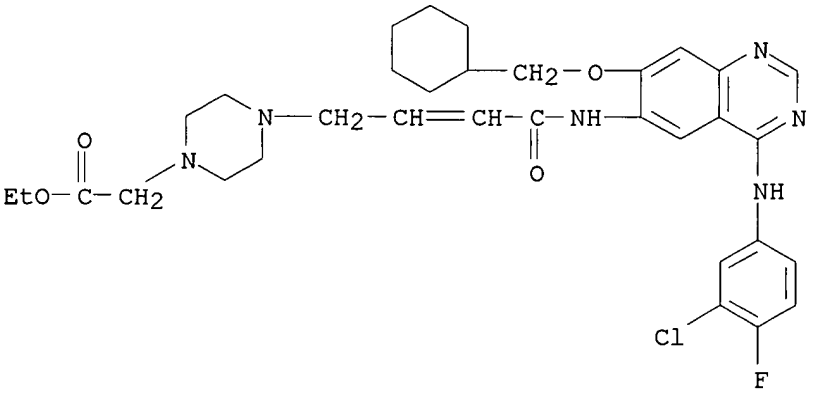
RN 290301-98-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-7-methoxy-6-quinazolinyl]-4-(2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)



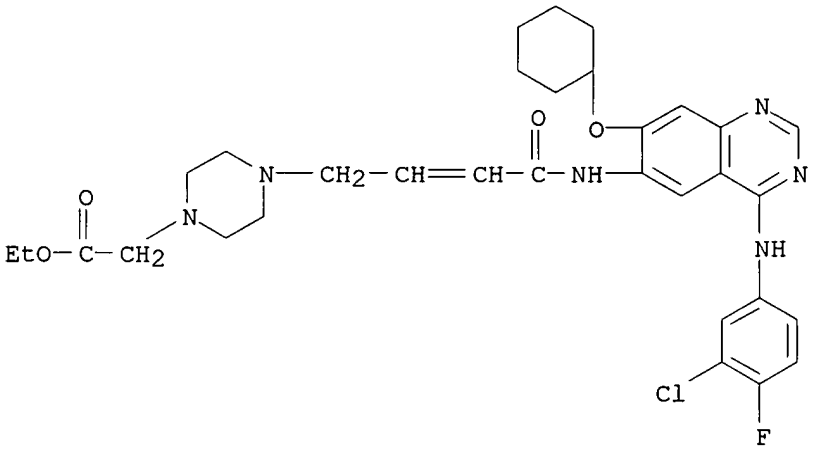
RN 290302-21-5 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



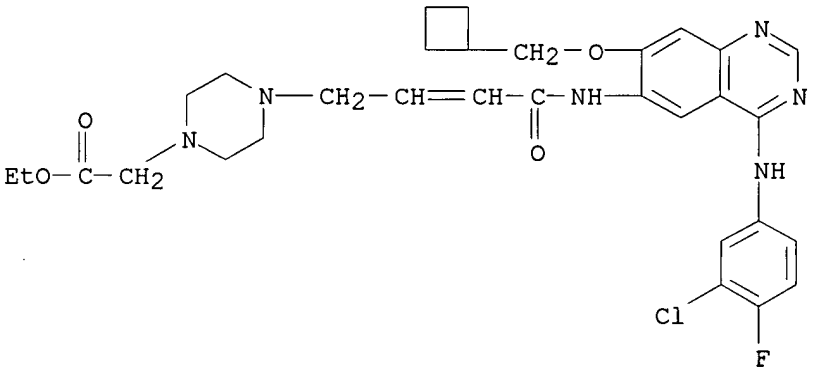
RN 290302-29-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclohexylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



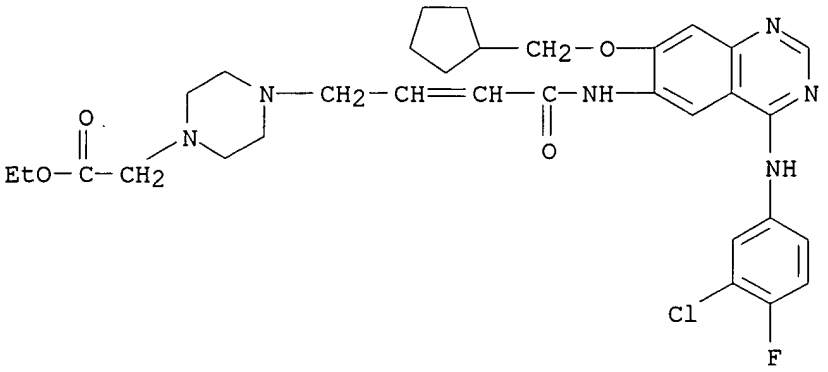
RN 290302-31-7 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclohexyloxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



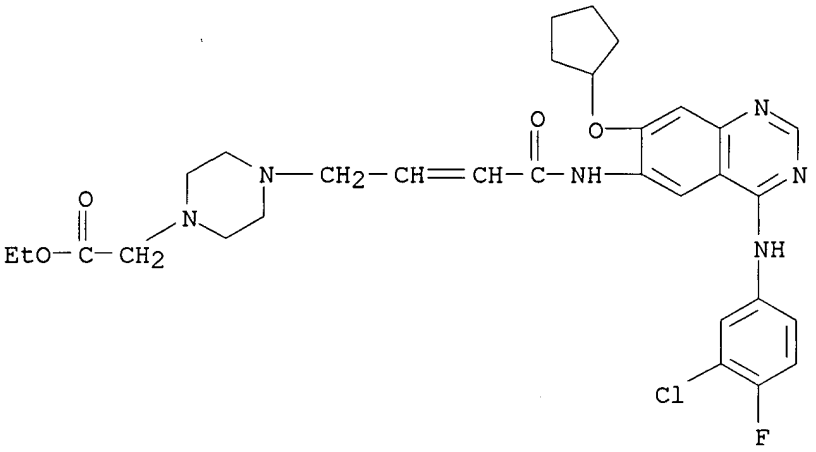
RN 290302-35-1 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



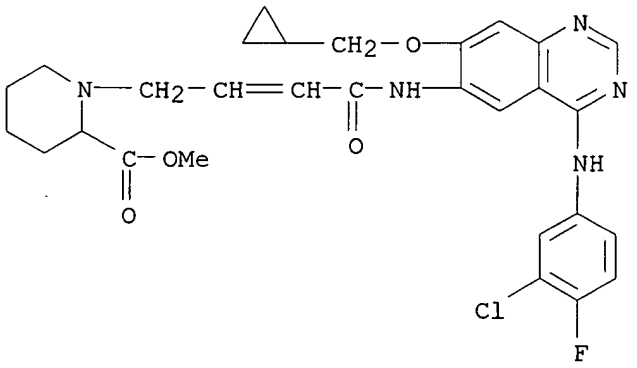
RN 290302-37-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



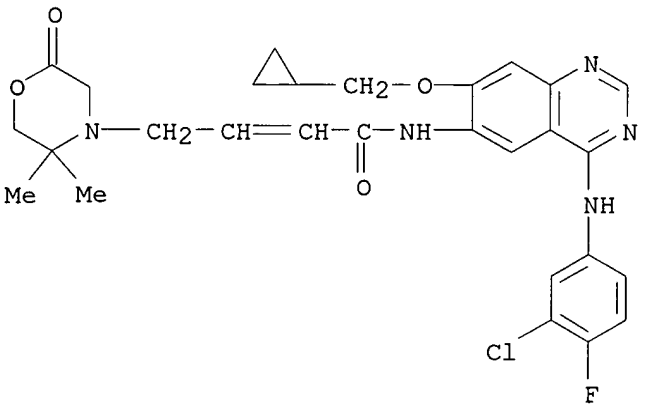
RN 290302-41-9 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopentyloxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



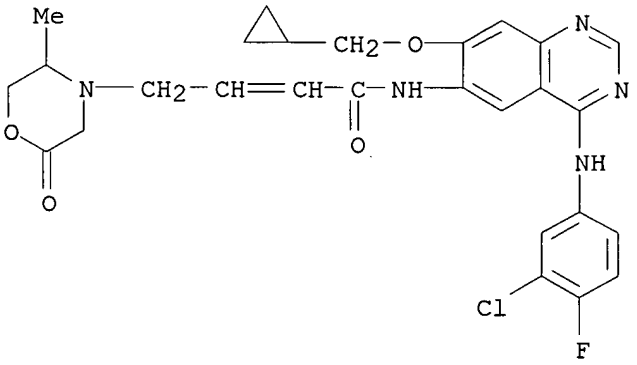
RN 290302-45-3 CAPLUS
CN 2-Piperidinecarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 290302-51-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(5,5-dimethyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

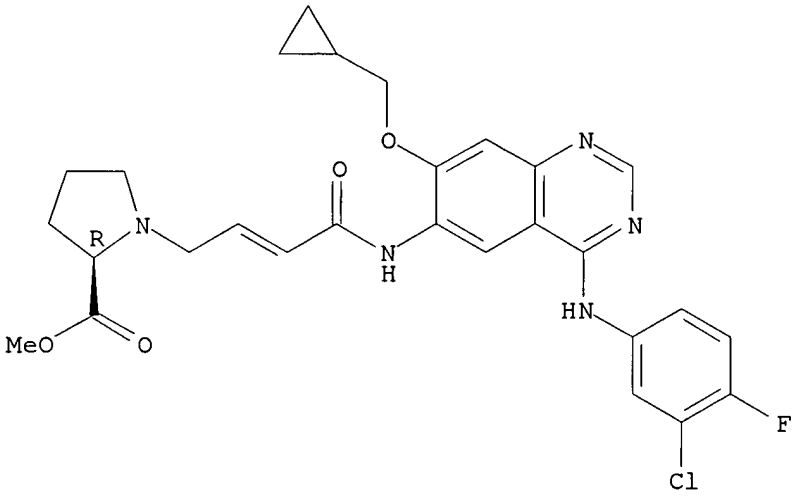


RN 290302-53-3 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(5-methyl-2-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)



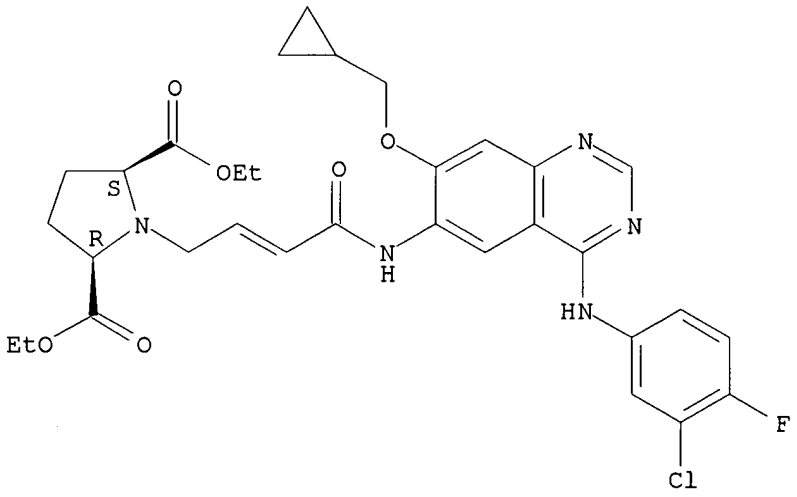
RN 290302-55-5 CAPLUS
CN D-Proline, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



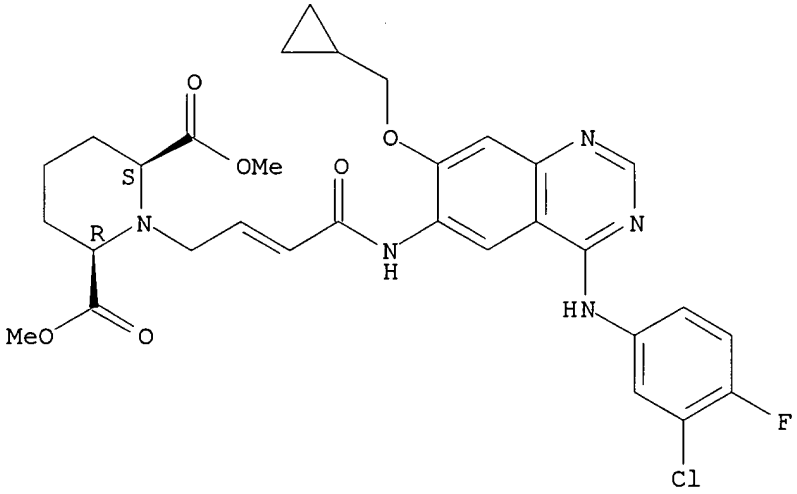
RN 290302-57-7 CAPLUS
CN 2,5-Pyrrolidinedicarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, diethyl ester, (2R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.



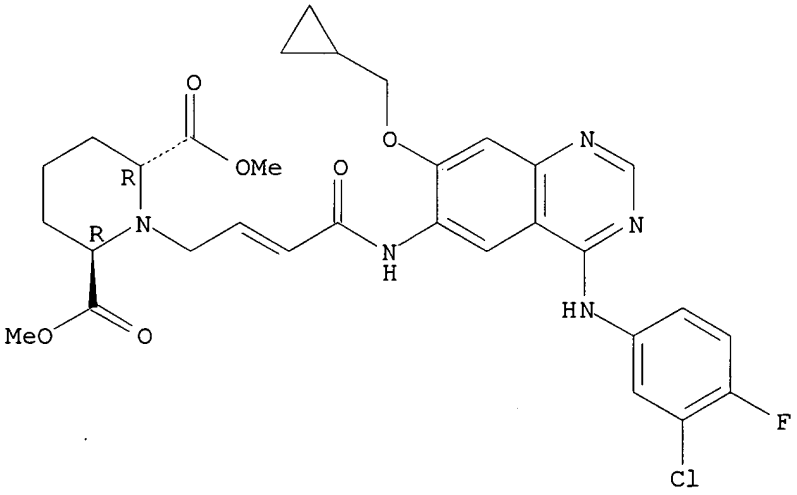
RN 290302-59-9 CAPLUS
CN 2,6-Piperidinedicarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, dimethyl ester, (2R,6S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.



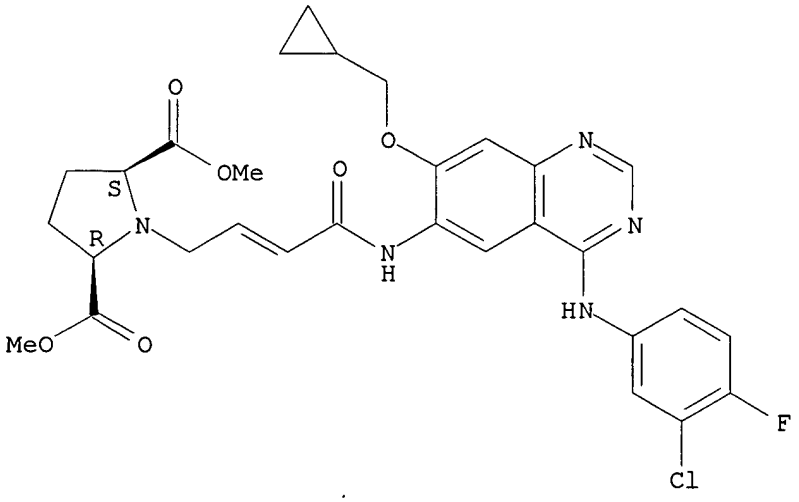
RN 290302-61-3 CAPLUS
CN 2,6-Piperidinedicarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, dimethyl ester, (2R,6R)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.



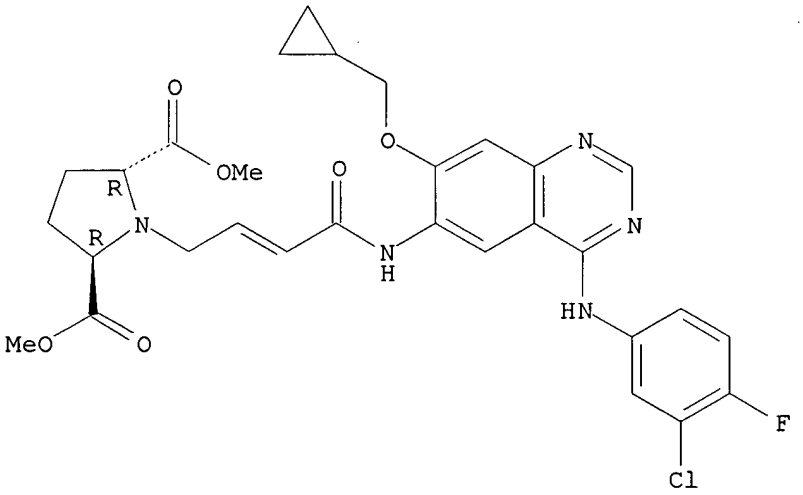
RN 290302-63-5 CAPLUS
CN 2,5-Pyrrolidinedicarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, dimethyl ester, (2R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry unknown.

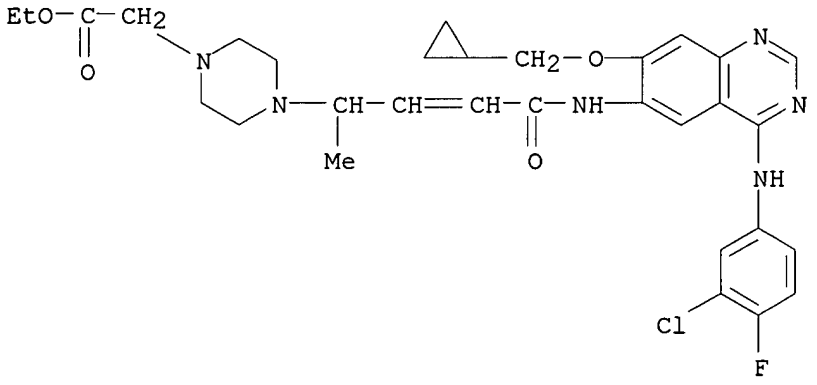


RN 290302-65-7 CAPLUS
CN 2,5-Pyrrolidinedicarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, dimethyl ester, (2R,5R)-rel- (9CI) (CA INDEX NAME)

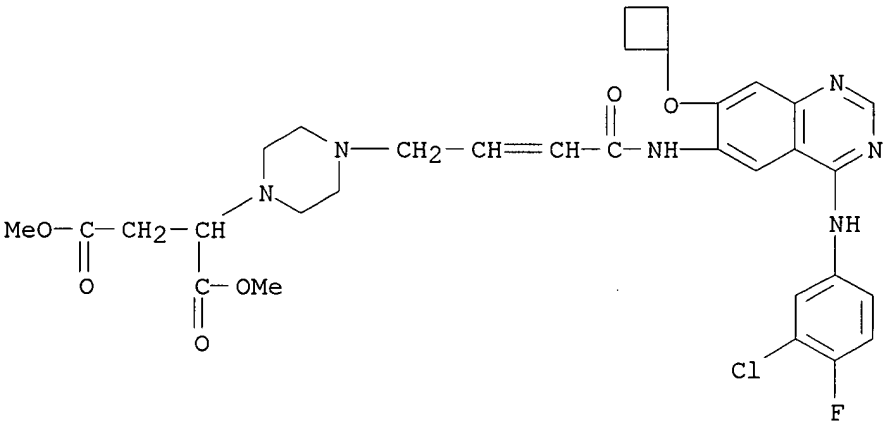
Relative stereochemistry.
Double bond geometry unknown.



RN 290302-67-9 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-1-methyl-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

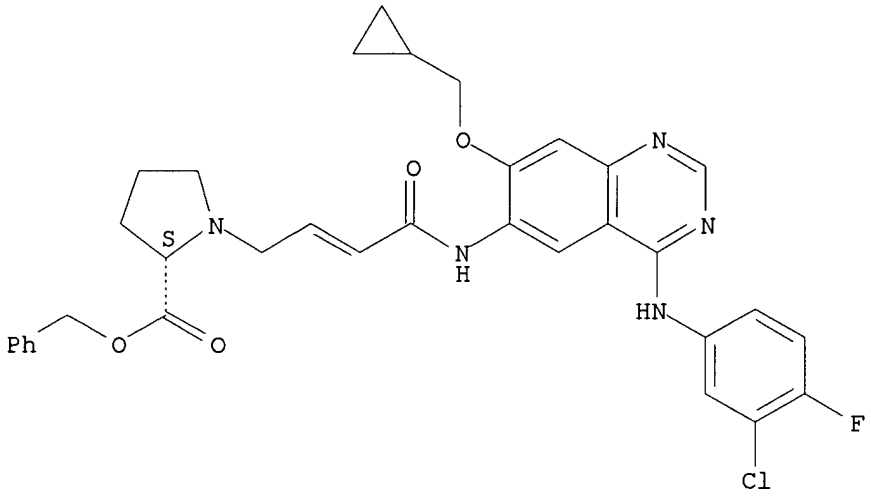


RN 290302-69-1 CAPLUS
CN Butanedioic acid, [4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclobutyloxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-1-piperazinyl]-, dimethyl ester (9CI) (CA INDEX NAME)



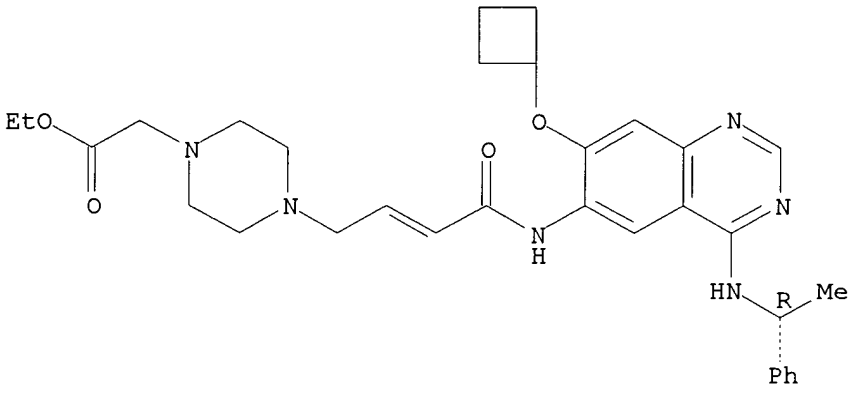
RN 290302-73-7 CAPLUS
CN L-Proline, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



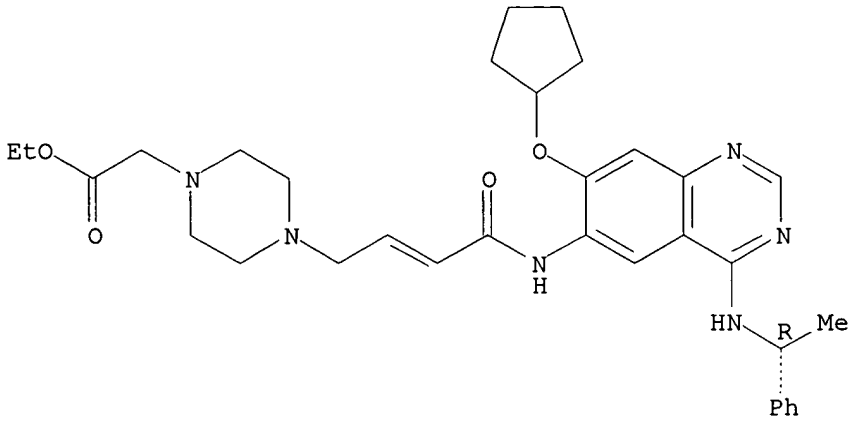
RN 290302-75-9 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclobutyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



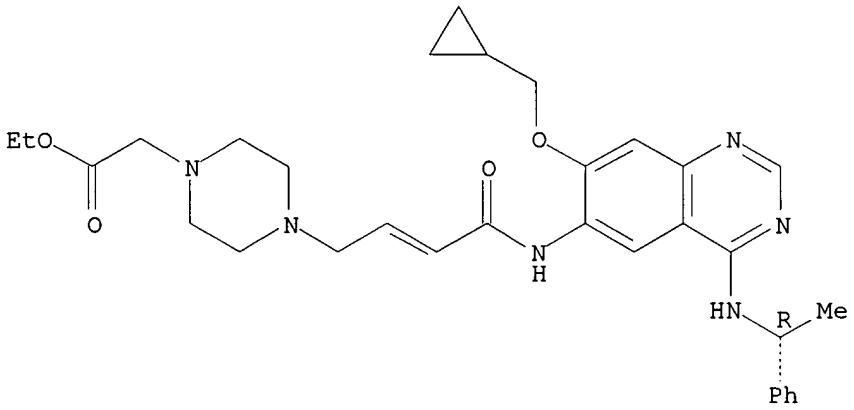
RN 290302-77-1 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclopentyloxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

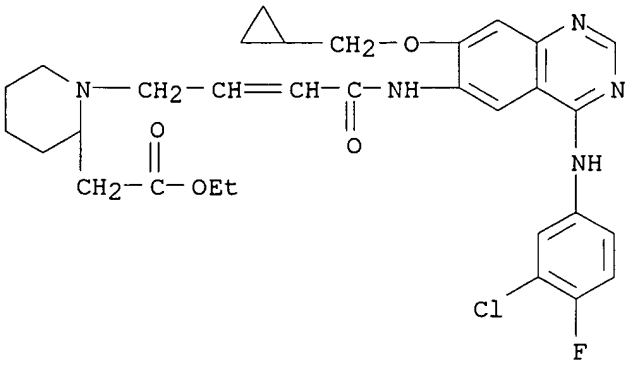


RN 290302-79-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclopropylmethoxy)-4-[[(1R)-1-phenylethyl]amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

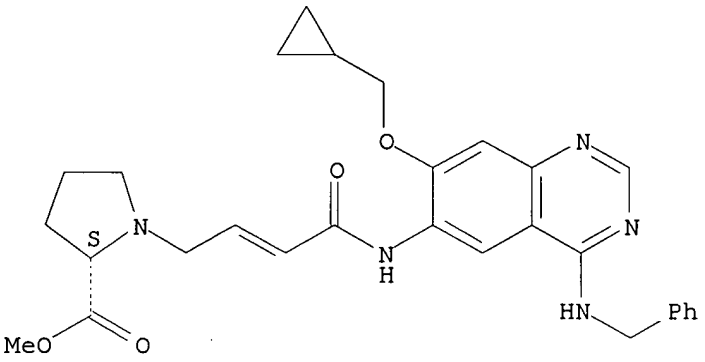


RN 290302-81-7 CAPLUS
CN 2-Piperidineacetic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)

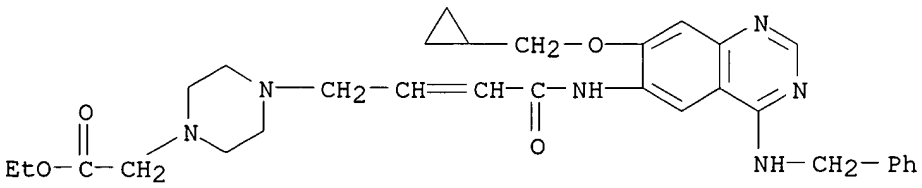


RN 290302-85-1 CAPLUS
CN L-Proline, 1-[4-[[7-(cyclopropylmethoxy)-4-[(phenylmethyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, methyl ester (9CI) (CA INDEX NAME)

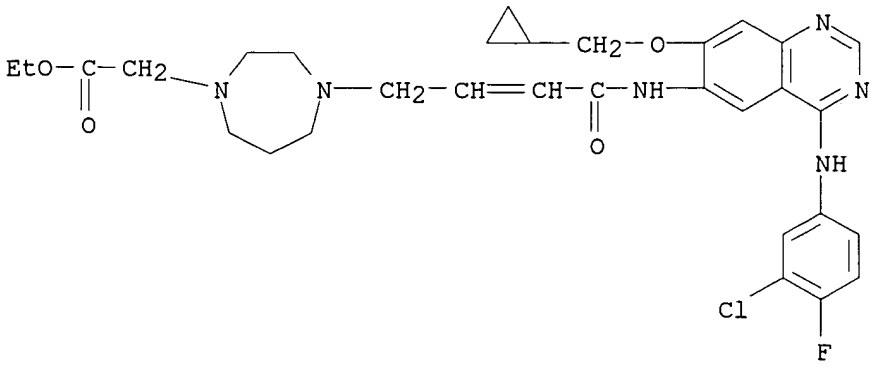
Absolute stereochemistry.
Double bond geometry unknown.



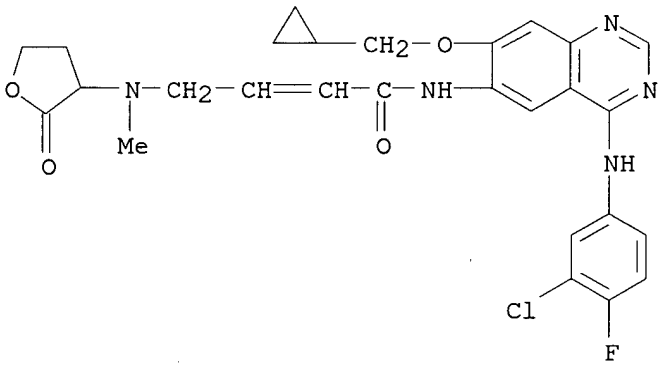
RN 290302-87-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[7-(cyclopropylmethoxy)-4-[(phenylmethyl)amino]-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



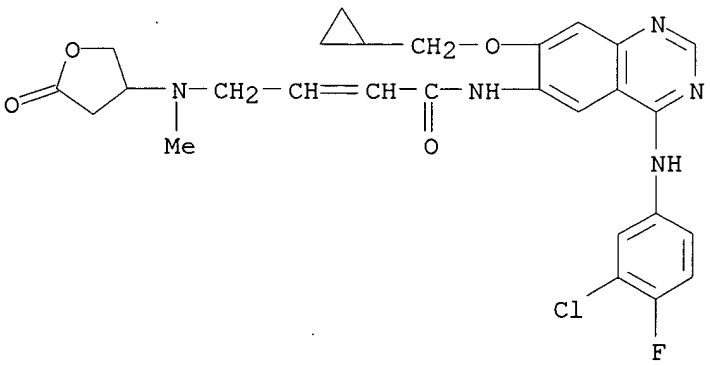
RN 290302-91-9 CAPLUS
CN 1H-1,4-Diazepine-1-acetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]hexahydro-, ethyl ester (9CI) (CA INDEX NAME)



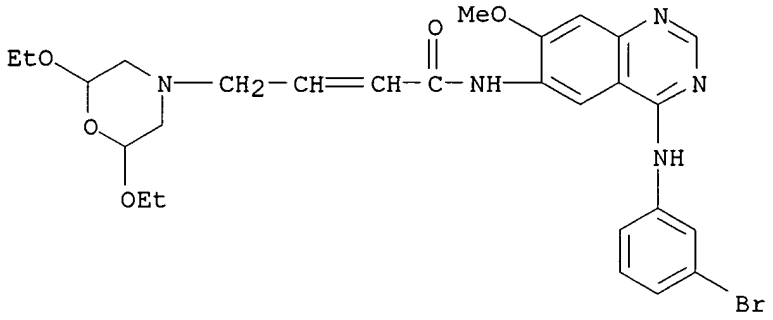
RN 290302-93-1 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl(tetrahydro-2-oxo-3-furanyl)amino]- (9CI) (CA INDEX NAME)



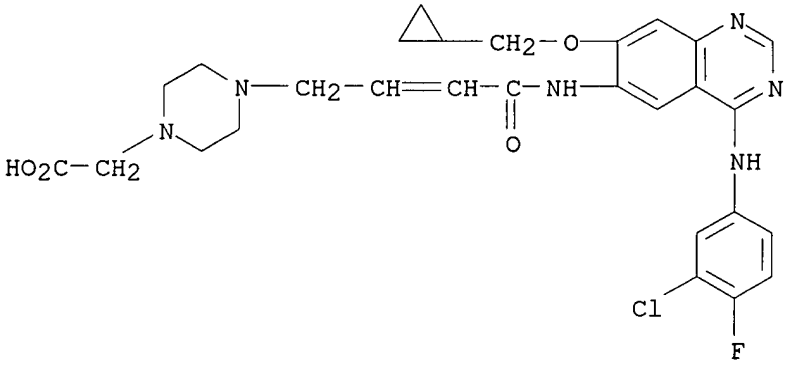
RN 290302-94-2 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[methyl(tetrahydro-5-oxo-3-furanyl)amino]- (9CI) (CA INDEX NAME)



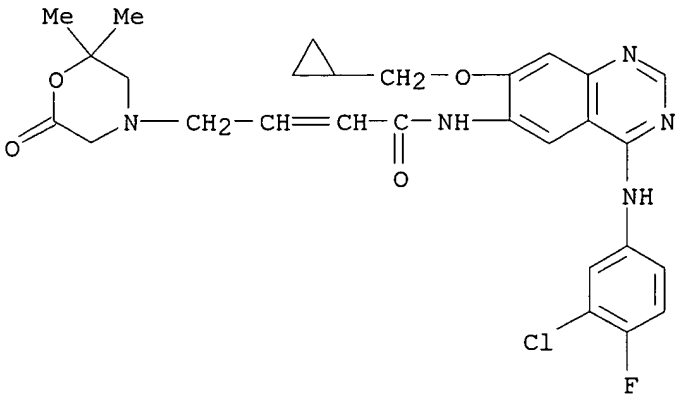
RN 290302-96-4 CAPLUS
CN 2-Butenamide, N-[4-[(3-bromophenyl)amino]-7-methoxy-6-quinazolinyl]-4-(2,6-diethoxy-4-morpholinyl)- (9CI) (CA INDEX NAME)



RN 290303-00-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]- (9CI) (CA INDEX NAME)

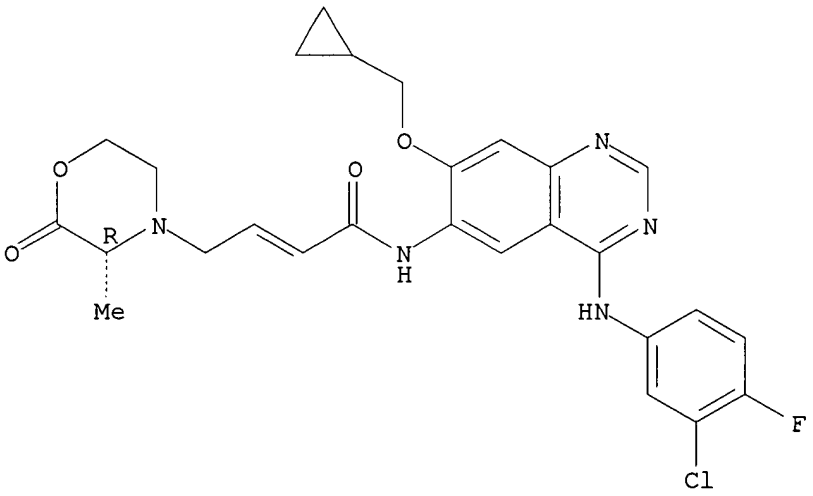


RN 290303-02-5 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-(2,2-dimethyl-6-oxo-4-morpholinyl)- (9CI) (CA INDEX NAME)

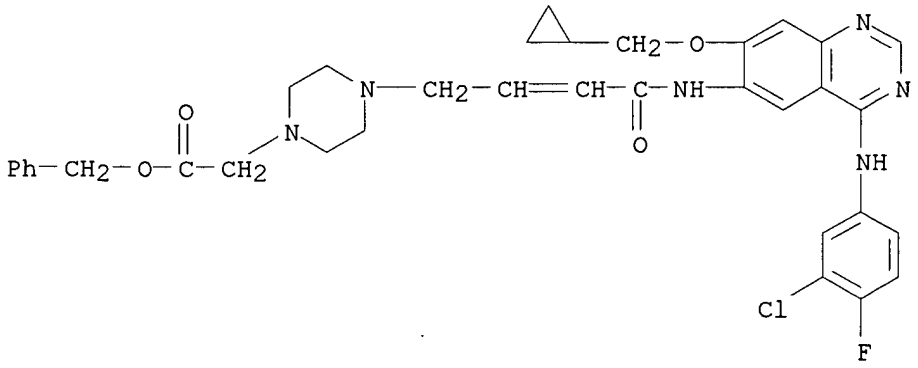


RN 290303-03-6 CAPLUS
CN 2-Butenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]-4-[(3R)-3-methyl-2-oxo-4-morpholinyl]- (9CI) (CA INDEX NAME)

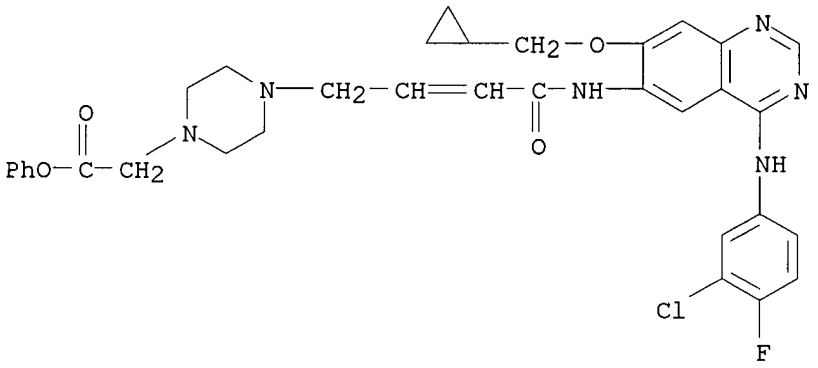
Absolute stereochemistry.
Double bond geometry unknown.



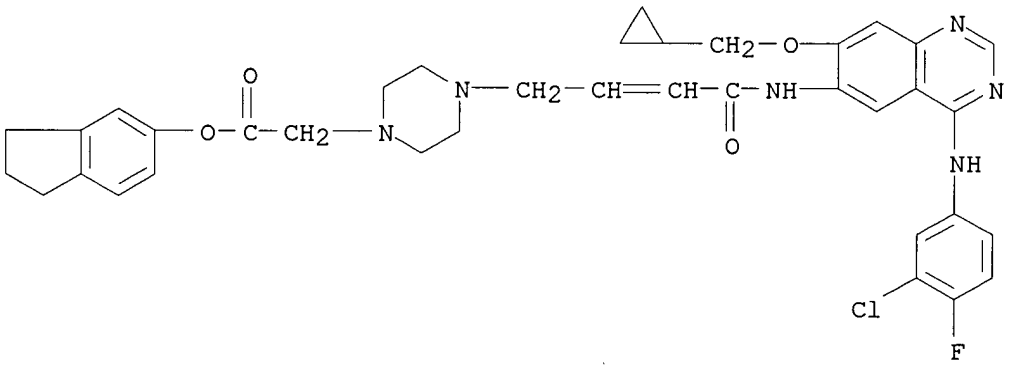
RN 290303-05-8 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



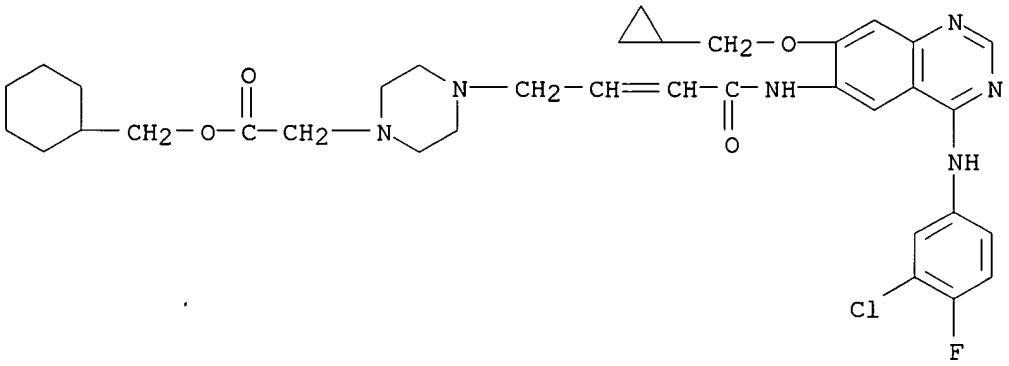
RN 290303-06-9 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, phenyl ester (9CI) (CA INDEX NAME)



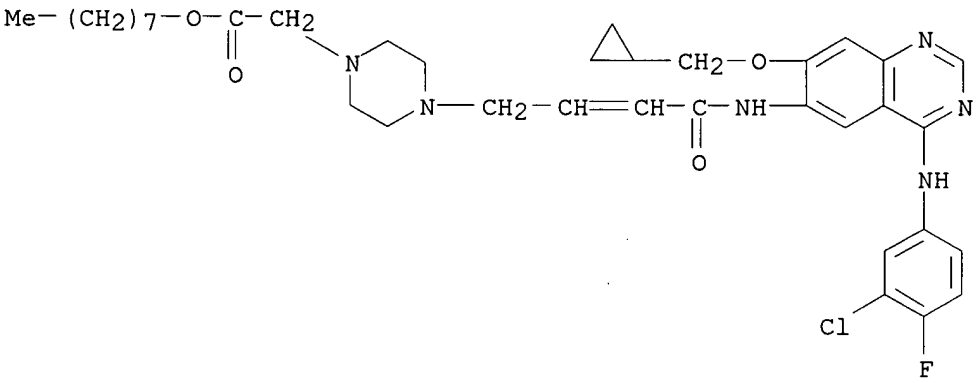
RN 290303-07-0 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, 2,3-dihydro-1H-inden-5-yl ester (9CI) (CA INDEX NAME)



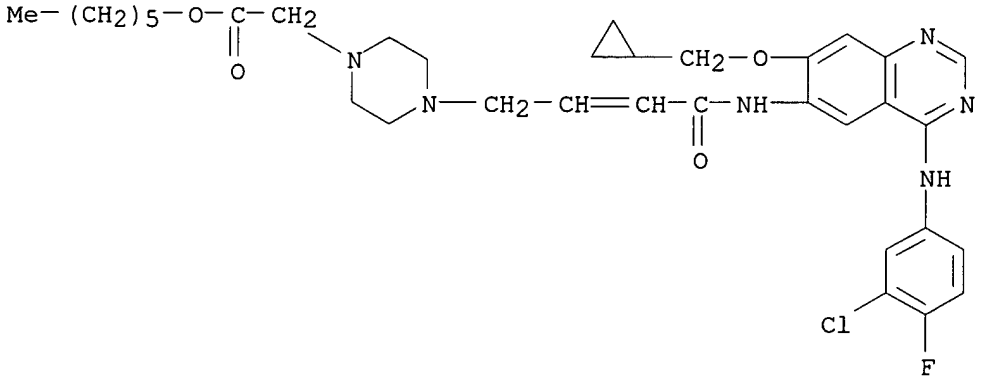
RN 290303-08-1 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, cyclohexylmethyl ester (9CI) (CA INDEX NAME)



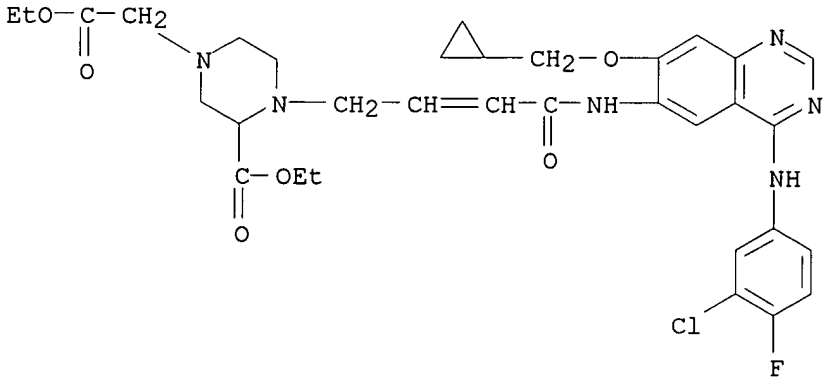
RN 290303-09-2 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, octyl ester (9CI) (CA INDEX NAME)



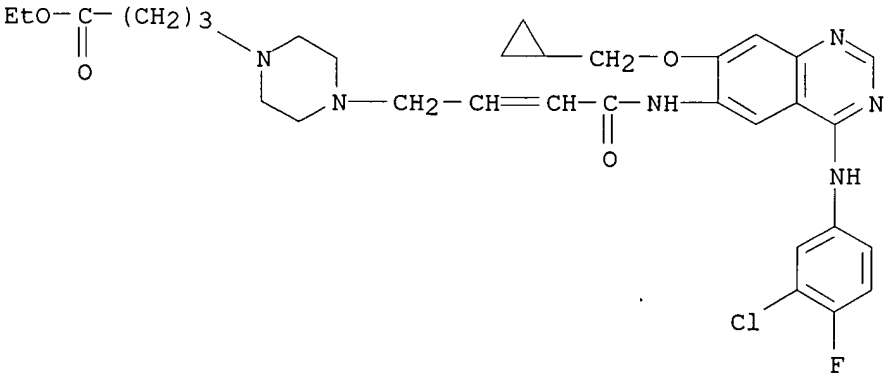
RN 290303-10-5 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, hexyl ester (9CI) (CA INDEX NAME)



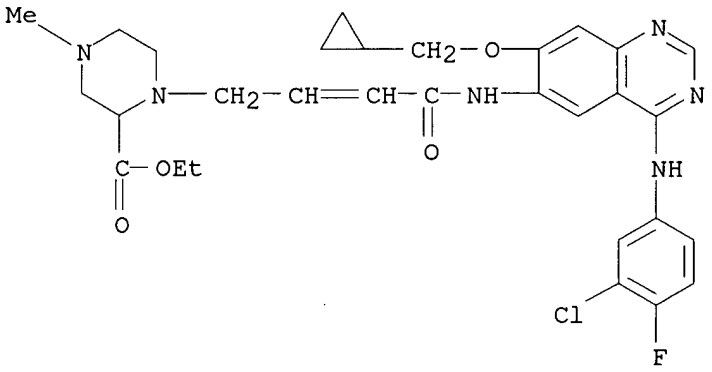
RN 290303-11-6 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-3-(ethoxycarbonyl)-, ethyl ester (9CI) (CA INDEX NAME)



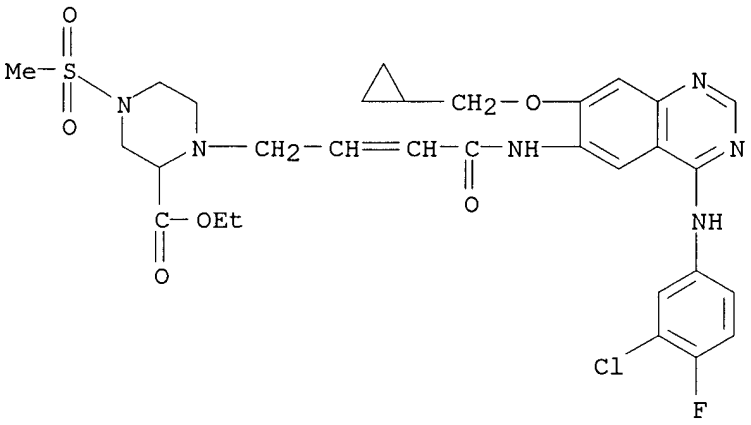
RN 290303-12-7 CAPLUS
CN 1-Piperazinebutanoic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



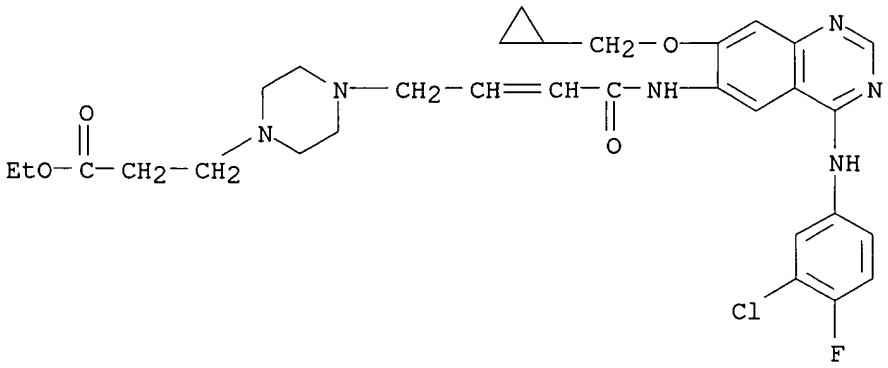
RN 290303-14-9 CAPLUS
CN 2-Piperazinecarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-methyl-, ethyl ester (9CI) (CA INDEX NAME)



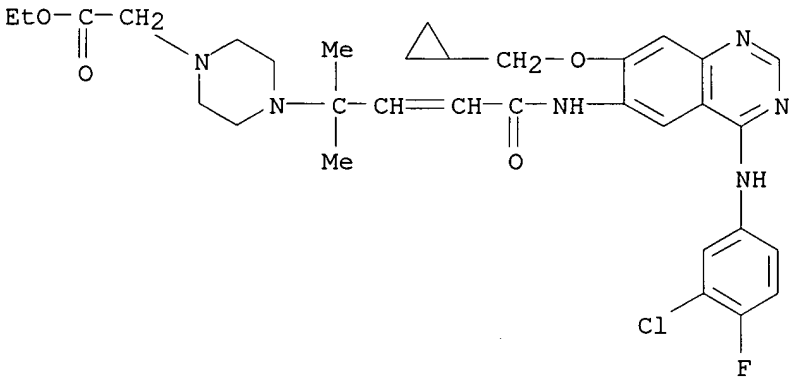
RN 290303-15-0 CAPLUS
CN 2-Piperazinecarboxylic acid, 1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-4-(methylsulfonyl)-, ethyl ester (9CI) (CA INDEX NAME)



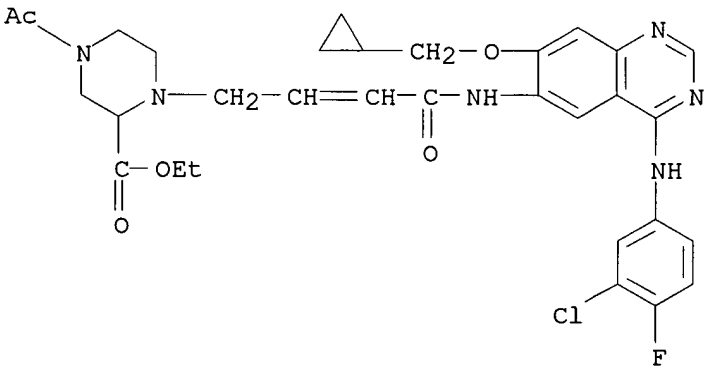
RN 290303-16-1 CAPLUS
CN 1-Piperazinepropanoic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 290303-17-2 CAPLUS
CN 1-Piperazineacetic acid, 4-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-1,1-dimethyl-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 290303-18-3 CAPLUS
CN 2-Piperazinecarboxylic acid, 4-acetyl-1-[4-[[4-[(3-chloro-4-fluorophenyl)amino]-7-(cyclopropylmethoxy)-6-quinazolinyl]amino]-4-oxo-2-butenyl]-, ethyl ester (9CI) (CA INDEX NAME)



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

see 179 27

L17 ANSWER 18 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:607393 CAPLUS
DN 133:207916
TI Preparation of aminoquinazolines as epidermal growth factor receptor inhibitors.
IN Himmelsbach, Frank; Langkopf, Elke; Jung, Birgit; Metz, Thomas
PA Boehringer Ingelheim Pharma K-G, Germany
SO Ger. Offen., 26 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19908567	A1	20000831	DE 1999-19908567	19990227
	CA 2361174	AA	20000908	CA 2000-2361174	20000224
	WO 2000051991	A1	20000908	WO 2000-EP1496	20000224
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	NO 2001004114	A	20011015	NO 2001-4114	20010824
PRAI	DE 1999-19908567	A	19990227		
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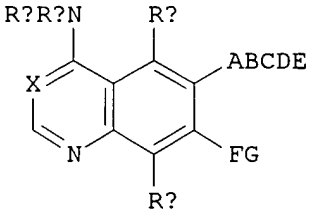


I

AB Title compds. [I; Ra = H, alkyl; Rb = (substituted) Ph, PhCH2, 1-phenylethyl; Rc, Rm = H, F, Cl, MeO, (methoxy-, dimethylamino-,

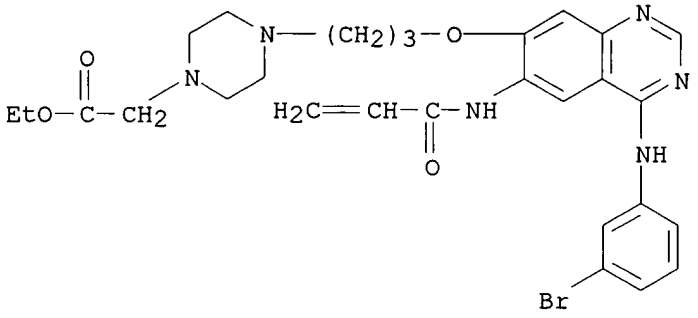
diethylamino-, pyrrolidino-, piperidino-, morpholino- substituted) Me; X = N, NCC; A = O, alkylimino; B = CO, SO2; C = (Me- or F3C-substituted) allenylene, vinylene; D = (fluorinated) alkylene, carbonylalkylene, sulfonylalkylene, etc.; E, G = (substituted) R6O2CYNR5, etc.; R5 = H, (substituted) alkyl; R6 = H, (substituted) alkyl, cycloalkyl, alkenyl, alkynyl, etc.; F = alkylene, oxyalkylene, O; FG = H, F, Cl, alkoxy, etc.], were prepd. Thus, 6-amino-4-[(3-bromophenyl)amino]-7-[3-[4-(ethoxycarbonyl)methylpiperazin-1-yl]propoxy]quinazoline (prepn. given) in CH2Cl2 contg. Et3N was treated with acryloyl chloride in CH2Cl2 at -10.degree. to give 62% 4-[(3-bromophenyl)amino]-7-[3-[4-[(ethoxycarbonyl)methyl]piperazin-1-yl]propyloxy]-6-[(vinylcarbonyl)amino]quinazoline. The latter inhibited EGF-dependent proliferation with IC50 = 2.6 nM.

IT **289700-58-9P 289700-59-0P 289700-60-3P 289700-61-4P 289700-62-5P 289700-63-6P 289700-64-7P 289700-65-8P 289700-66-9P 289700-67-0P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of aminoquinazolines as epidermal growth factor receptor inhibitors)

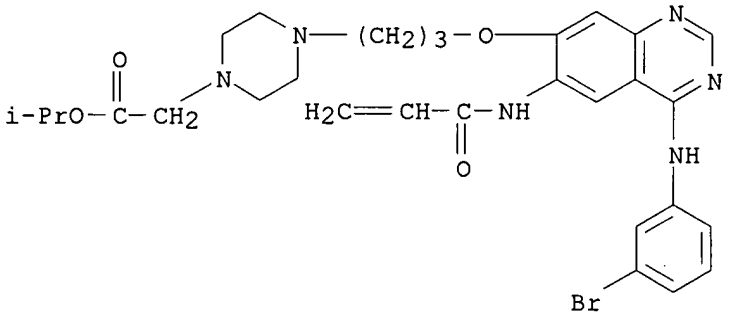
RN 289700-58-9 CAPLUS

CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)

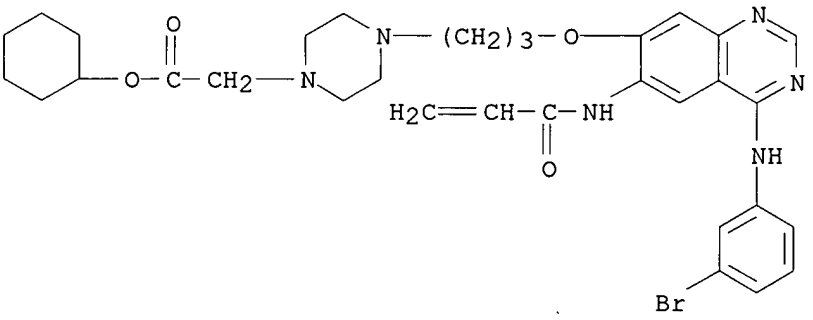


RN 289700-59-0 CAPLUS

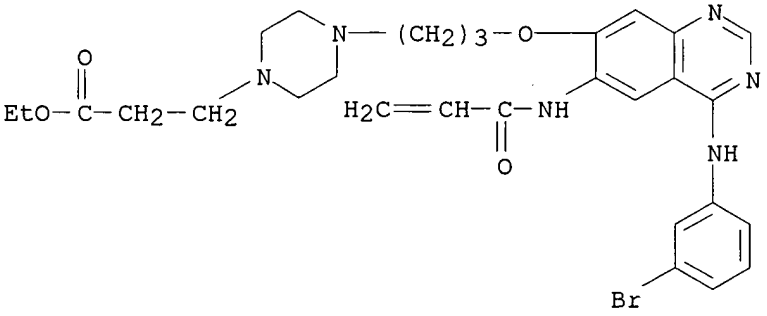
CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, 1-methylethyl ester (9CI) (CA INDEX NAME)



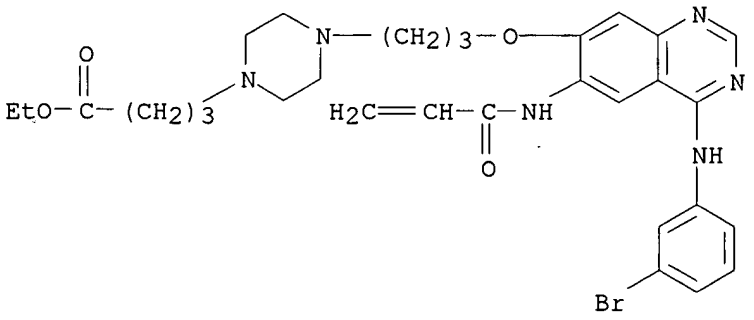
RN 289700-60-3 CAPLUS
CN 1-Piperazineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, cyclohexyl ester (9CI) (CA INDEX NAME)



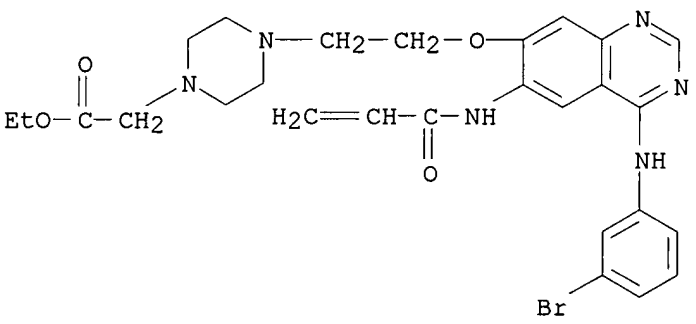
RN 289700-61-4 CAPLUS
CN 1-Piperazinepropanoic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



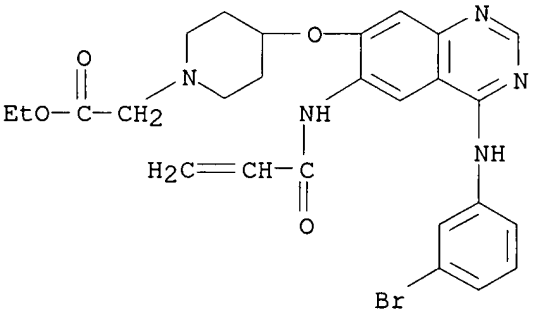
RN 289700-62-5 CAPLUS
CN 1-Piperazinebutanoic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



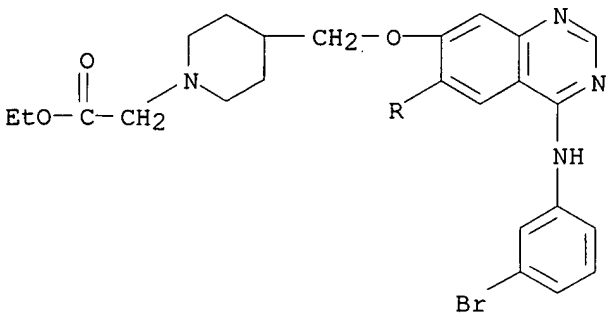
RN 289700-63-6 CAPLUS
CN 1-Piperazineacetic acid, 4-[2-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]ethyl]-, ethyl ester (9CI) (CA INDEX NAME)

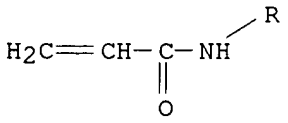


RN 289700-64-7 CAPLUS
CN 1-Piperidineacetic acid, 4-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]-, ethyl ester (9CI) (CA INDEX NAME)

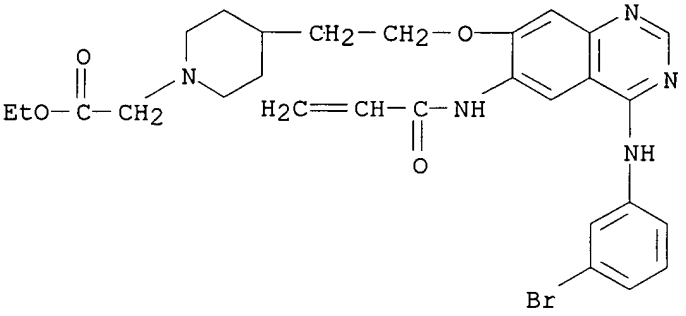


RN 289700-65-8 CAPLUS
CN 1-Piperidineacetic acid, 4-[[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]methyl]-, ethyl ester (9CI) (CA INDEX NAME)

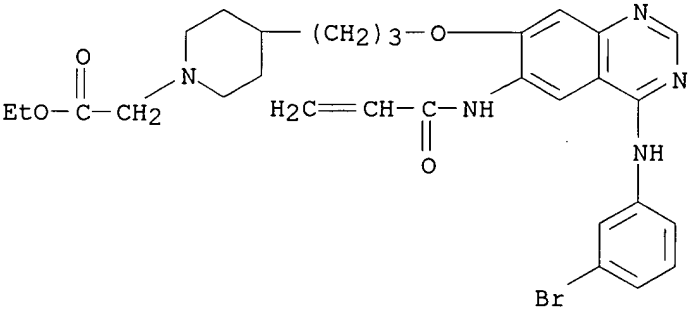




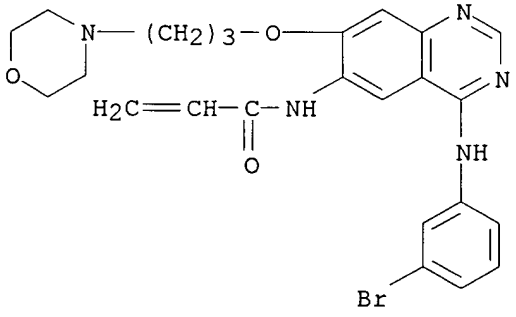
RN 289700-66-9 CAPLUS
CN 1-Piperidineacetic acid, 4-[2-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]ethyl]-, ethyl ester (9CI) (CA INDEX NAME)



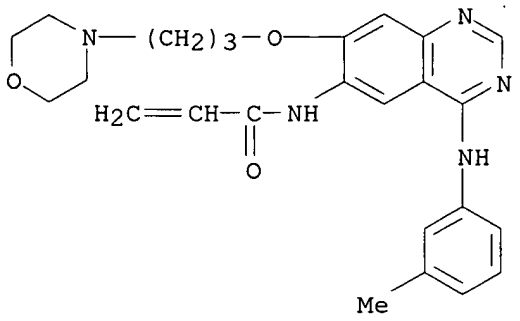
RN 289700-67-0 CAPLUS
CN 1-Piperidineacetic acid, 4-[3-[[4-[(3-bromophenyl)amino]-6-[(1-oxo-2-propenyl)amino]-7-quinazolinyl]oxy]propyl]-, ethyl ester (9CI) (CA INDEX NAME)



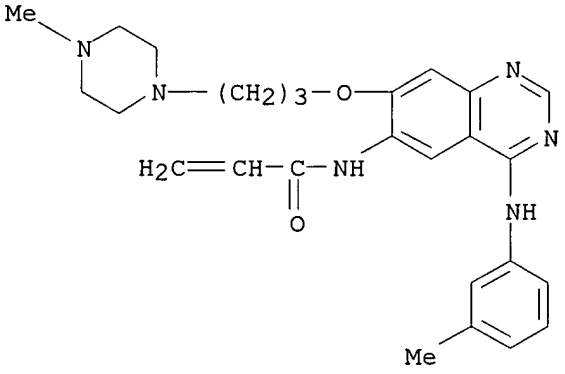
L17 ANSWER 19 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:481416 CAPLUS
DN 134:216784
TI Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. [Erratum to document cited in CA132:317628]
AU Smaill, Jeff B.; Rewcastle, Gordon W.; Bridges, Alexander J.; Zhou, Hairong; Showalter, H. D. Hollis; Fry, David W.; Nelson, James M.; Sherwood, Veronika; Elliott, William L.; Vincent, Patrick W.; DeJohn, Dana E.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Denny, William A.
CS Auckland Cancer Society Research Centre, Faculty Medical and Health Sciences, The Univ. Auckland, Auckland, N. Z.
SO Journal of Medicinal Chemistry (2000), 43(16), 3199
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB Six author names were inadvertently omitted from the author contribution line. The complete author list is as follows: Jeff B. Smaill, Gordon W. Rewcastle, Alexander J. Bridges, Hairong Zhou, H. D. Hollis Showalter, David W. Fry, James M. Nelson, Veronika Sherwood, William L. Elliott, Patrick W. Vincent, Dana E. DeJohn, Joseph A. Loo, Kenneth D. Greis, O. Helen Chan, Eric L. Reyner, Elke Lipka, and William A. Denny.
IT **198959-99-8P 198960-00-8P 198960-01-9P 198960-02-0P 198960-04-2P 267243-27-6P 267243-28-7P**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines (Erratum))
RN 198959-99-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



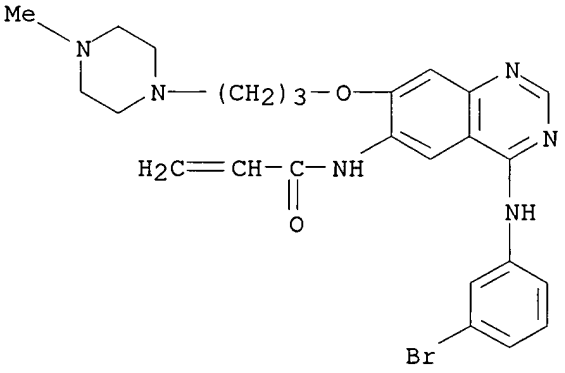
RN 198960-00-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



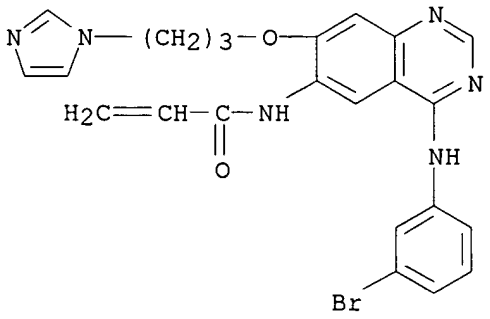
RN 198960-01-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



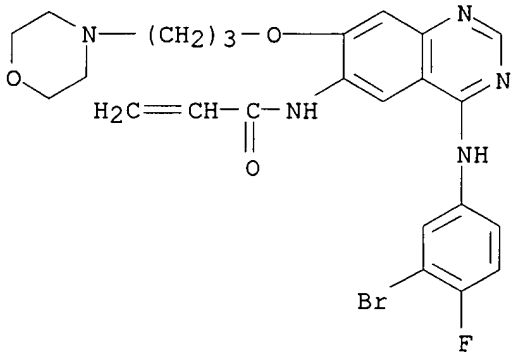
RN 198960-02-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



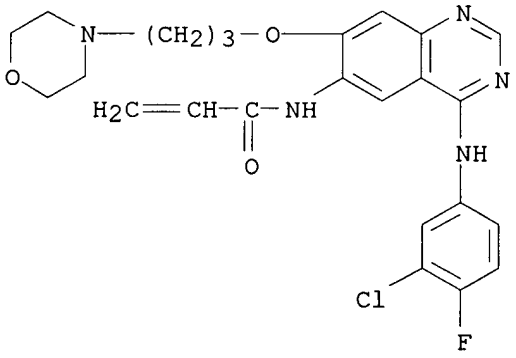
RN 198960-04-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1H-imidazol-1-yl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 267243-27-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromo-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



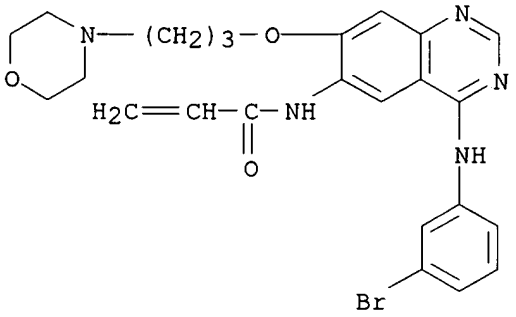
L17 ANSWER 20 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:368316 CAPLUS
DN 133:4672
TI Preparation of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases
IN Bridges, Alexander James; Driscoll, Denise; Klohs, Wayne Daniel
PA Warner-Lambert Co., USA
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000031048	A1	20000602	WO 1999-US22116	19990923
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9962612	A1	20000613	AU 1999-62612	19990923
	BR 9915487	A	20010731	BR 1999-15487	19990923
	EP 1131304	A1	20010912	EP 1999-949821	19990923
	EP 1131304	B1	20021204		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002530386	T2	20020917	JP 2000-583876	19990923
	EE 200100271	A	20021015	EE 2001-271	19990923
	AT 229008	E	20021215	AT 1999-949821	19990923
	US 6344455	B1	20020205	US 2001-831991	20010516
	NO 2001002465	A	20010713	NO 2001-2465	20010518
	BG 105608	A	20020131	BG 2001-105608	20010615
PRAI	US 1998-109065P	P	19981119		
	WO 1999-US22116	W	19990923		

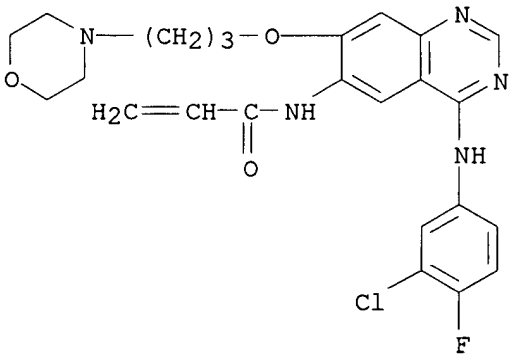
AB The title compd. that is an irreversible inhibitor of tyrosine kinases such as EGFR, erbB2, and erbB4, and inhibitor of the tyrosine phosphorylation of erbB3 and VEGF secretion (biol. data were given), was prepd. The title compd. is useful in treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis.

IT **198959-99-8P 267243-28-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-{4-(3-chloro-4-fluorophenylamino)-7-[3-(morpholin-4-yl)propoxy]quinazolin-6-yl}acrylamide as an irreversible inhibitor of tyrosine kinases)

RN 198959-99-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

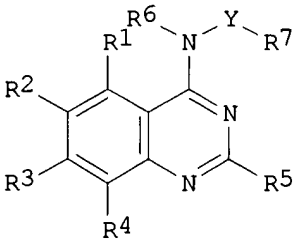


RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

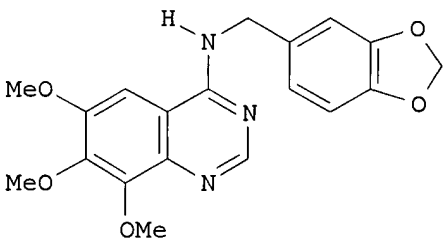
L17 ANSWER 21 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:220729 CAPLUS
DN 132:251161
TI Preparation of 4-aminoquinazolines for treating a patient having a precancerous lesions
IN Pamukcu, Rifat; Piazza, Gary
PA Cell Pathways, Inc., USA
SO U.S., 54 pp., Cont. of U.S. Ser. No. 475,197, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6046206	A	20000404	US 1997-846593	19970430
PRAI US 1995-475197		19950607		

OS MARPAT 132:251161
GI



I

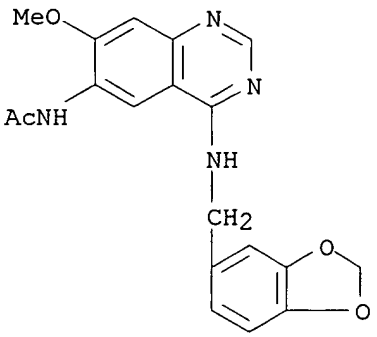


II

AB The title compds. [I; R1-R4 = H, alkoxy, hydroxyalkyl, etc.; R5 = H, halo, OH, etc.; R6 = H, alkyl, acyl, etc.; R7 = H, OH, CN, etc.; Y = (un)substituted (CH2)q (q = 1-8), CO], useful for the treatment of patients having precancerous lesions, and also for inhibiting the growth of neoplastic cells (no data), were prepd. Thus, reacting 4-chloro-6,7,8-trimethoxyquinazoline with piperonylamine in the presence of Na2CO3 in iso-PrOH afforded 69% II.

IT **150450-69-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 4-aminoquinazolines for treating a patient having a precancerous lesions)

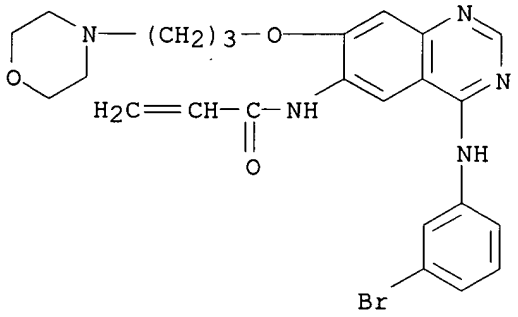
RN 150450-69-4 CAPLUS
CN Acetamide, N-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-7-methoxy-6-quinazolinyl]- (9CI) (CA INDEX NAME)



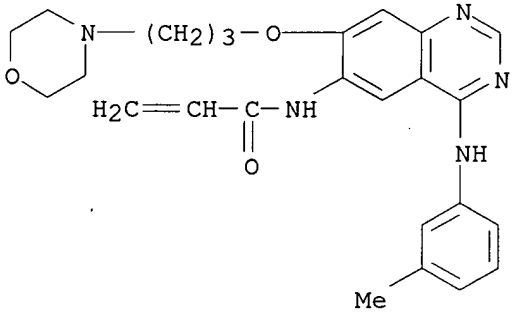
RE.CNT 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 22 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 2000:164843 CAPLUS
DN 132:317628
TI Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(Phenylamino)quinazoline- and 4-(Phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions
AU Smaill, Jeff B.; Rewcastle, Gordon W.; Loo, Joseph A.; Greis, Kenneth D.; Chan, O. Helen; Reyner, Eric L.; Lipka, Elke; Showalter, H. D. Hollis; Vincent, Patrick W.; Elliott, William L.; Denny, William A.
CS Auckland Cancer Society Research Centre Faculty of Medical and Health Sciences, The University of Auckland, Auckland, N. Z.
SO Journal of Medicinal Chemistry (2000), 43(7), 1380-1397
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
AB 4-Anilinoquinazoline- and 4-anilinopyrido[3,2-d]pyrimidine-6-acrylamides substituted with solubilizing 7-alkylamine or 7-alkoxyamine side chains were prepd. by reaction of the corresponding 6-amines with acrylic acid or acrylic acid anhydrides. In the pyrido[3,2-d]pyrimidine series, the intermediate 6-amino-7-alkylamines were prepd. from 7-bromo-6-fluoropyrido[3,2-d]pyrimidine via Stille coupling with the appropriate stannane under palladium(0) catalysis. This proved a versatile method for the introduction of cationic solubilizing side chains. The compds. were evaluated for their inhibition of phosphorylation of the isolated EGFR enzyme and for inhibition of EGF-stimulated autophosphorylation of EGFR in A431 cells and of heregulin-stimulated autophosphorylation of erbB2 in MDA-MB 453 cells. Quinazoline analogs with 7-alkoxyamine solubilizing groups were potent irreversible inhibitors of the isolated EGFR enzyme, with IC50[app] values from 2 to 4 nM, and potently inhibited both EGFR and erbB2 autophosphorylation in cells. 7-Alkylamino- and 7-alkoxyaminopyrido[3,2-d]pyrimidines were also irreversible inhibitors with equal or superior potency against the isolated enzyme but were less effective in the cellular autophosphorylation assays. Both quinazoline- and pyrido[3,2-d]pyrimidine-6-acrylamides bound at the ATP site alkylating cysteine 773, as shown by electrospray ionization mass spectrometry, and had similar rates of absorptive and secretory transport in Caco-2 cells. A comparison of two 7-propoxymorpholide analogs showed that the pyrido[3,2-d]pyrimidine-6-acrylamide had greater amide instability and higher acrylamide reactivity, being converted to glutathione adducts in cells more rapidly than the corresponding quinazoline. This difference may contribute to the obsd. lower cellular potency of the pyrido[3,2-d]pyrimidine-6-acrylamides. Selected compds. showed high in vivo activity against A431 xenografts on oral dosing, with the quinazolines being superior to the pyrido[3,2-d]pyrimidines. Overall, the quinazolines proved superior to previous analogs in terms of aq. soly., potency, and in vivo antitumor activity, and one example (CI 1033) has been selected for clin. evaluation.
IT **198959-99-8P 198960-00-8P 198960-01-9P**
198960-02-0P 198960-04-2P 267243-27-6P
267243-28-7P
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(antitumor and EGFR enzyme-inhibiting SAR of quinazolines)
RN 198959-99-8 CAPLUS

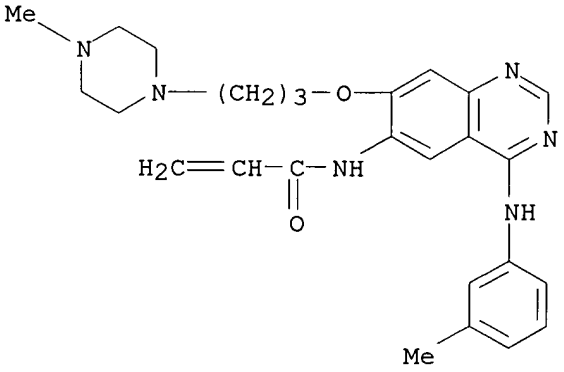
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



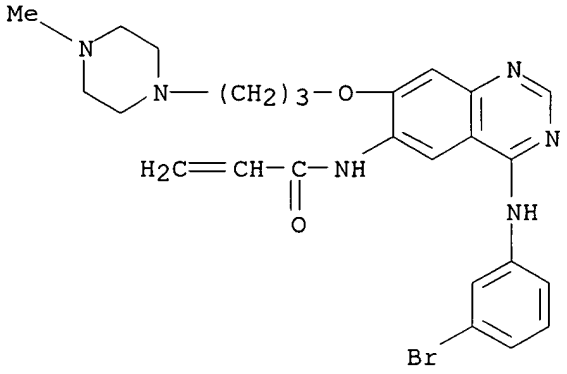
RN 198960-00-8 CAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



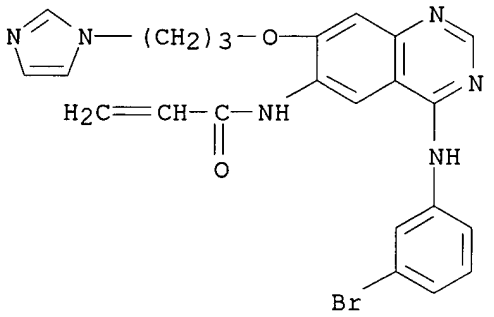
RN 198960-01-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



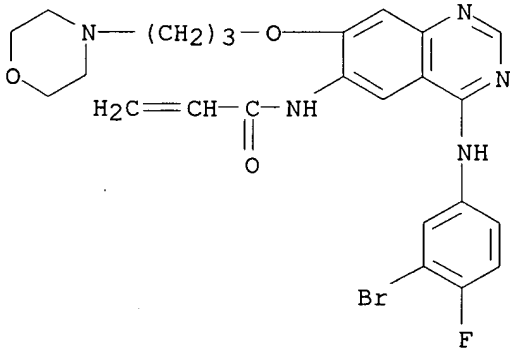
RN 198960-02-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



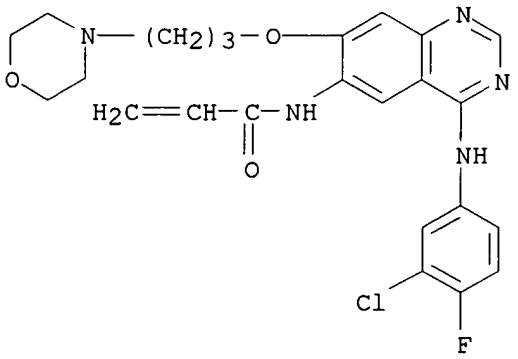
RN 198960-04-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1H-imidazol-1-yl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 267243-27-6 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromo-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 267243-28-7 CAPLUS
CN 2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

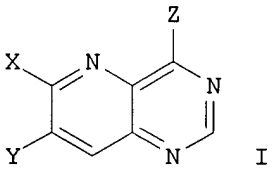


RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 1999:113672 CAPLUS
DN 130:182476
TI Preparation of heterocyclic compounds as irreversible bicyclic inhibitors of tyrosine kinases
IN Bridges, Alexander James
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9906396	A1	19990211	WO 1998-US15592	19980729
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9886659	A1	19990222	AU 1998-86659	19980729
	US 6153617	A	20001128	US 1999-269647	19990325
	US 2003087881	A1	20030508	US 2002-272651	20021017
PRAI	US 1997-54061P	P	19970729		
	WO 1998-US15592	W	19980729		
	US 1999-269647	A3	19990325		
	US 2000-656331	B1	20000906		

OS MARPAT 130:182476
GI



I

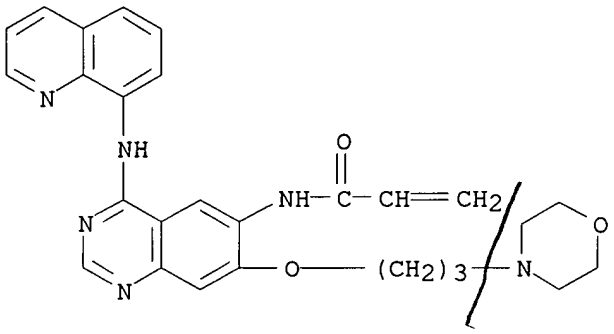
AB The title compds., e.g. I [X = DEF, Y = SR4, etc. ; or X = SR4, etc., and Y = DEF; D = O, etc.; E = CO, etc.; F = CR1(:C):C(R5)H, etc.; a proviso is given; R1 = H, halo, etc.; R5 = H, halo, perfluoroalkyl, etc.; Z = indoline moiety (generic structure given), etc.; R4 = H, alkyl, etc.], are prepd. This invention also provides a method of treating cancer, restenosis, atherosclerosis, endometriosis, and psoriasis and a pharmaceutical compn. that comprises a compd. that is an irreversible inhibitor of tyrosine kinases. N-[4-(6-bromo-2,3-dihydroindol-1-yl)quinazolin-6-yl]acrylamide in vitro showed IC50 of 0.4 nM against epidermal growth factor receptor tyrosine kinase.

IT **220576-91-0P 220576-92-1P 220576-93-2P**
220576-94-3P 220577-98-0P 220578-00-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of heterocyclic compds. as irreversible bicyclic inhibitors of

tyrosine kinases)

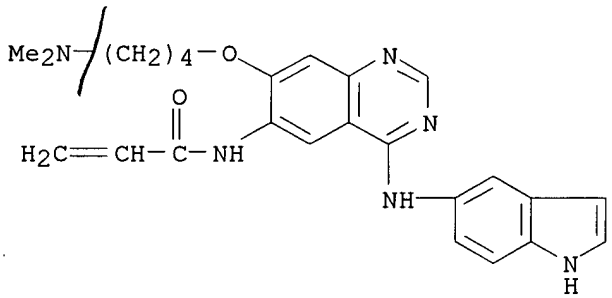
RN 220576-91-0 CAPLUS

CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-(8-quinolinylamino)-6-quinazolinyl]- (9CI) (CA INDEX NAME)



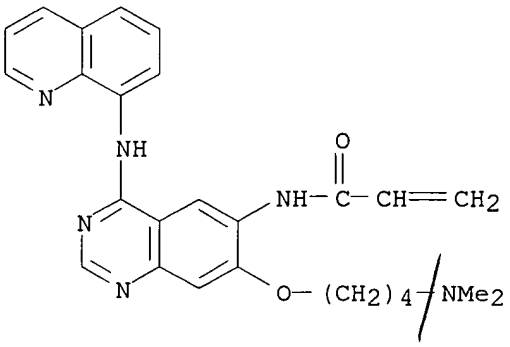
RN 220576-92-1 CAPLUS

CN 2-Propenamide, N-[7-[4-(dimethylamino)butoxy]-4-(1H-indol-5-ylamino)-6-quinazolinyl]- (9CI) (CA INDEX NAME)



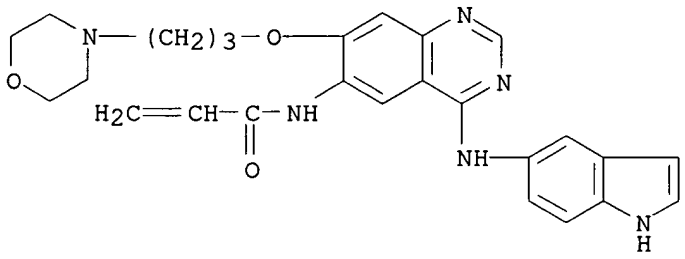
RN 220576-93-2 CAPLUS

CN 2-Propenamide, N-[7-[4-(dimethylamino)butoxy]-4-(8-quinolinylamino)-6-quinazolinyl]- (9CI) (CA INDEX NAME)

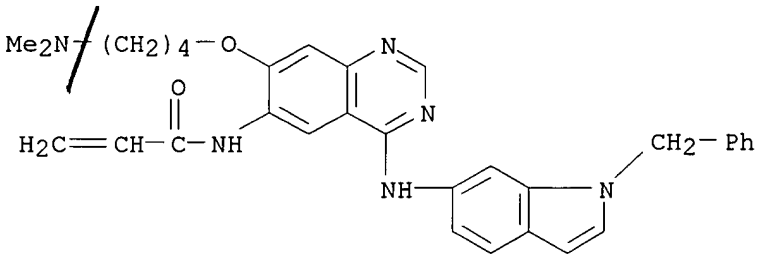


RN 220576-94-3 CAPLUS

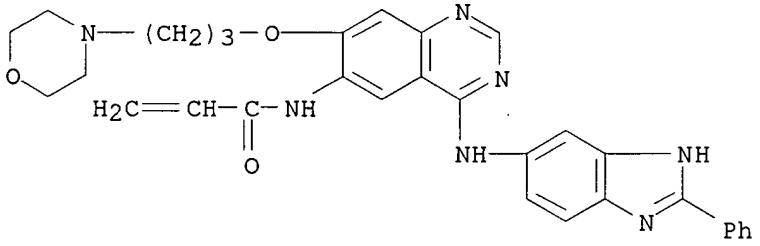
CN 2-Propenamide, N-[4-(1H-indol-5-ylamino)-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 220577-98-0 CAPLUS
CN 2-Propenamide, N-[7-[4-(dimethylamino)butoxy]-4-[[1-(phenylmethyl)-1H-indol-6-yl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 220578-00-7 CAPLUS
CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-[(2-phenyl-1H-benzimidazol-5-yl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

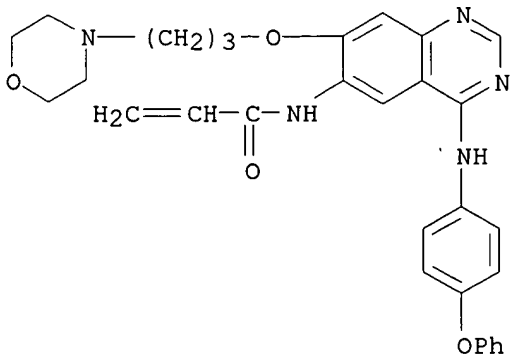


RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

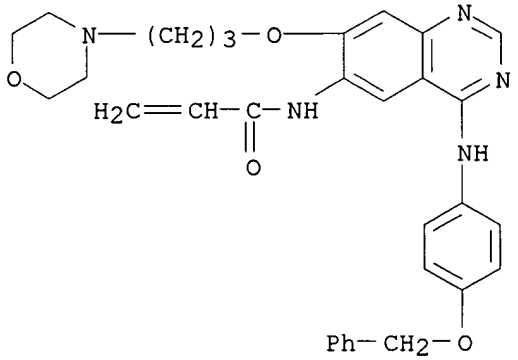
L17 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 1999:113656 CAPLUS
DN 130:168387
TI Irreversible inhibitors of tyrosine kinases
IN Bridges, Alexander James
PA Warner-Lambert Company, USA
SO PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9906378	A1	19990211	WO 1998-US15784	19980729
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9887607	A1	19990222	AU 1998-87607	19980729
	US 6127374	A	20001003	US 1999-269545	19990325
	US 6562818	B1	20030513	US 2000-593031	20000613
PRAI	US 1997-54060P	P	19970729		
	WO 1998-US15784	W	19980729		
	US 1999-269545	A3	19990325		

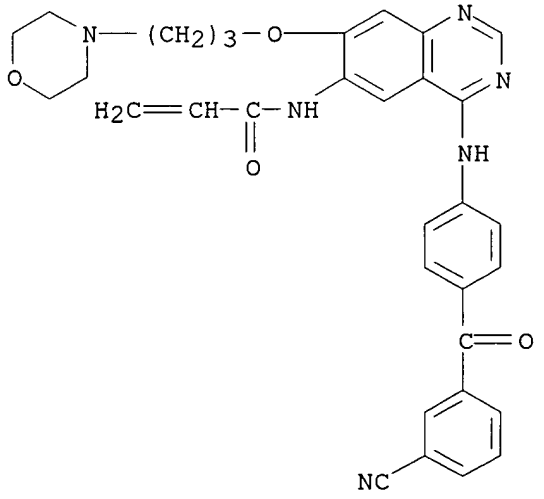
OS MARPAT 130:168387
AB Pyrimidine derivs. that are irreversible inhibitors of tyrosine kinases are reported. Thus, PhCH2OH was treated with 4-FC6H4NO2 to give 4-PhCH2OC6H4NO2, which was reduced to the amine and used to aminate 4-chloro-6-nitroquinazoline hydrochloride. The resulting 6-nitro-4-(4-benzyloxyanilino)quinazoline hydrochloride was reduced to the amine and acylated to give N-[4-(4-benzyloxyanilino)quinazolin-6-yl]acrylamide (I). I had an IC50 for inhibition of epidermal growth factor receptor tyrosine kinase of 3.6 nM.
IT **220488-46-0P 220488-49-3P 220489-87-2P**
220489-89-4P 220489-90-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of anilinoquinazolinylacrylamides and related compds. as tyrosine kinase inhibitors)
RN 220488-46-0 CAPLUS
CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-[(4-phenoxyphenyl)amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



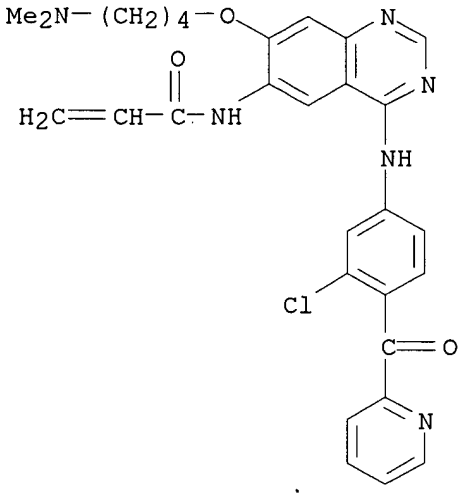
RN 220488-49-3 CAPLUS
CN 2-Propenamide, N-[7-[3-(4-morpholinyl)propoxy]-4-[[4-(phenylmethoxy)phenyl]amino]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



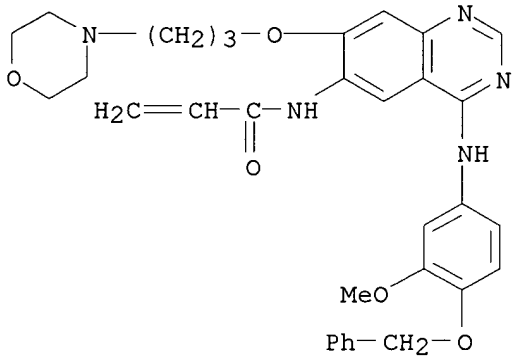
RN 220489-87-2 CAPLUS
CN 2-Propenamide, N-[4-[[4-(3-cyanobenzoyl)phenyl]amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 220489-89-4 CAPLUS
CN 2-Propenamide, N-[4-[[3-chloro-4-(2-pyridinylcarbonyl)phenyl]amino]-7-[4-(dimethylamino)butoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 220489-90-7 CAPLUS
CN 2-Propenamide, N-[4-[[3-methoxy-4-(phenylmethoxy)phenyl]amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

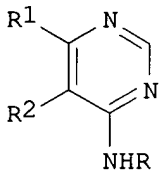


RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

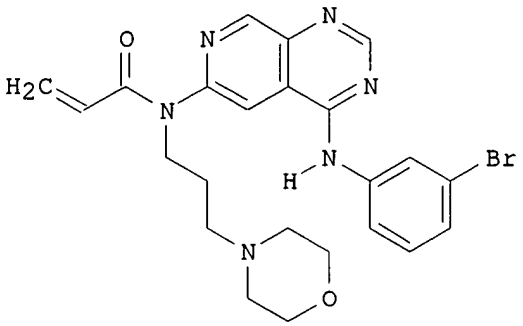
L17 ANSWER 25 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 1997:696745 CAPLUS
DN 128:3695
TI Preparation of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors
IN Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; Mcnamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong; et al.
PA Warner-Lambert Company, USA; Bridges, Alexander James; Denny, William Alexander; Dobrusin, Ellen Myra; Doherty, Annette Marian; Fry, David W.; Mcnamara, Dennis Joseph; Showalter, Howard Daniel Hollis; Smaill, Jeffrey B.; Zhou, Hairong
SO PCT Int. Appl., 193 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9738983	A1	19971023	WO 1997-US5778	19970408
	W: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2249446	AA	19971023	CA 1997-2249446	19970408
	AU 9724463	A1	19971107	AU 1997-24463	19970408
	AU 725533	B2	20001012		
	EP 892789	A1	19990127	EP 1997-920213	19970408
	EP 892789	B1	20020227		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
	CN 1218456	A	19990602	CN 1997-194458	19970408
	BR 9708640	A	19990803	BR 1997-8640	19970408
	JP 2000508657	T2	20000711	JP 1997-537173	19970408
	JP 3370340	B2	20030127		
	AT 213730	E	20020315	AT 1997-920213	19970408
	ES 2174250	T3	20021101	ES 1997-920213	19970408
	ZA 9703060	A	19971104	ZA 1997-3060	19970410
	BG 63160	B1	20010531	BG 1998-102811	19981001
	NO 9804718	A	19981209	NO 1998-4718	19981009
	KR 2000005364	A	20000125	KR 1998-708086	19981010
	US 6344459	B1	20020205	US 1999-155501	19990608
PRAI	US 1996-15351P	P	19960412		
	WO 1997-US5778	W	19970408		

OS MARPAT 128:3695
GI



I



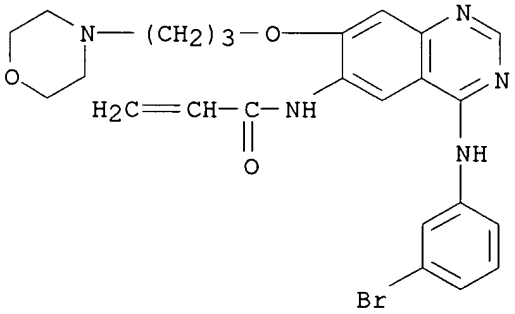
II

AB Title compds. [I; R = (CHR6)pR9; R1R2 = CH:CR7CR8:CH, CH:CR7CR8:N, CH:CR7N:CH, etc.; R6 = H or alkyl; 1 of R7,R8 = Z1Z2R10 and the other = OR4, SR4, NHR3; R3,R4 = (un)substituted alkyl, heterocyclylalkyl, etc.; R9 = (un)substituted Ph; R10 = CR11:CHR5, C.tplbond.CR5, CR11:C:CHR5; R5 = H, halo, alkyl, Ph, etc.; R11 = H, halo, alkyl; Z1 = bond, O, (alkyl)imino, CH2, etc.; Z2 = CO, SO, P(O)(OH), etc.; p = 0 or 1] were prepd. Thus, I (R = C6H4Br-3, R1R2 = CH:NCR8:CH, R8 = F) was condensed with 3-morpholinoprpanamine and the product acylated by CH2:CHCOCl to give title compd. II. Data for biol. activity of I were given.

IT **198959-99-8P 198960-00-8P 198960-01-9P 198960-02-0P 198960-04-2P 198960-61-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of N-quinazolinylacrylamides and analogs as tyrosine kinase inhibitors)

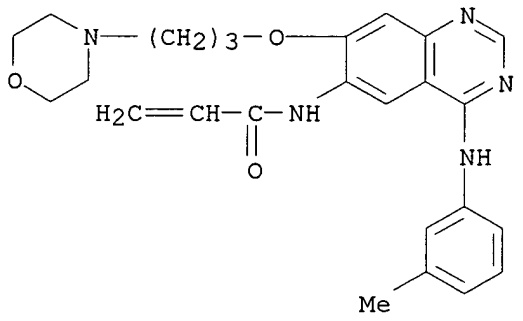
RN 198959-99-8 CAPLUS

CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)

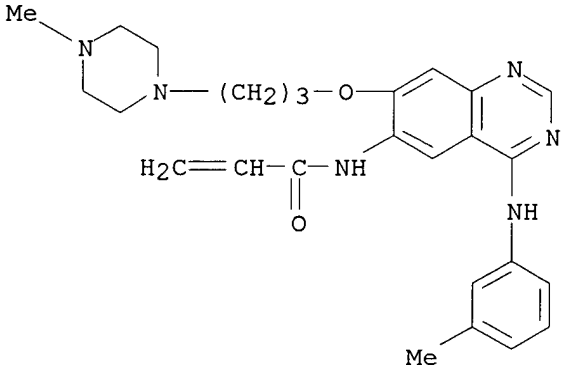


RN 198960-00-8 CAPLUS

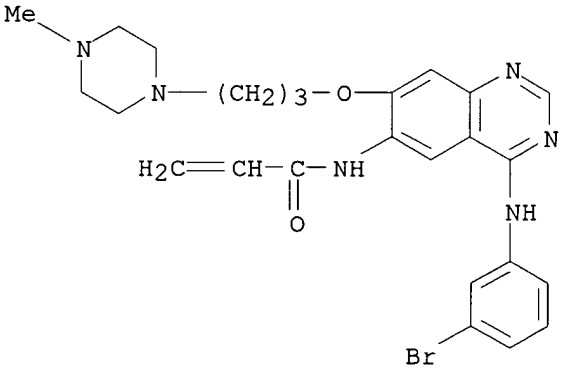
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



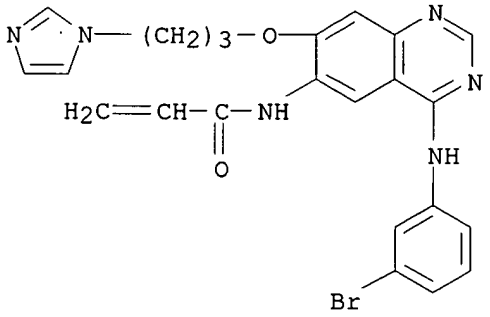
RN 198960-01-9 CAPLUS
CN 2-Propenamide, N-[4-[(3-methylphenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



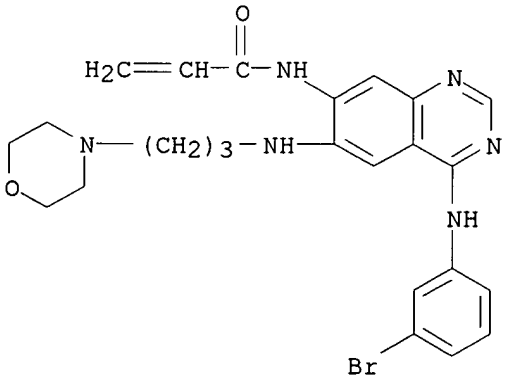
RN 198960-02-0 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(4-methyl-1-piperazinyl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



RN 198960-04-2 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-7-[3-(1H-imidazol-1-yl)propoxy]-6-quinazolinyl]- (9CI) (CA INDEX NAME)



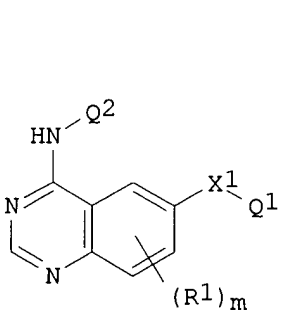
RN 198960-61-1 CAPLUS
CN 2-Propenamide, N-[4-[(3-bromophenyl)amino]-6-[[3-(4-morpholinyl)propyl]amino]-7-quinazolinyl]- (9CI) (CA INDEX NAME)



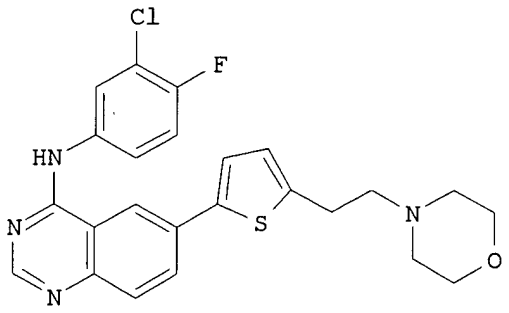
L17 ANSWER 26 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 1997:568090 CAPLUS
DN 127:248122
TI Quinazoline derivatives as antitumor agents
IN Barker, Andrew John; Johnstone, Craig
PA Zeneca Limited, UK
SO PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9730034	A1	19970821	WO 1997-GB344	19970210
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2242102	AA	19970821	CA 1997-2242102	19970210
	AU 9716126	A1	19970902	AU 1997-16126	19970210
	AU 707339	B2	19990708		
	EP 880507	A1	19981202	EP 1997-902496	19970210
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1211240	A	19990317	CN 1997-192242	19970210
	JP 2000504713	T2	20000418	JP 1997-529073	19970210
	NZ 330816	A	20000526	NZ 1997-330816	19970210
	ZA 9701231	A	19970814	ZA 1997-1231	19970213
	US 5866572	A	19990202	US 1997-796483	19970213
	NO 9803707	A	19981013	NO 1998-3707	19980813
	US 6399602	B1	20020604	US 1998-152070	19980911
	US 2003018029	A1	20030123	US 2002-136276	20020502
PRAI	GB 1996-3095	A	19960214		
	WO 1997-GB344	W	19970210		
	US 1997-796483	A3	19970213		
	US 1998-152070	A1	19980911		

OS MARPAT 127:248122
GI



I



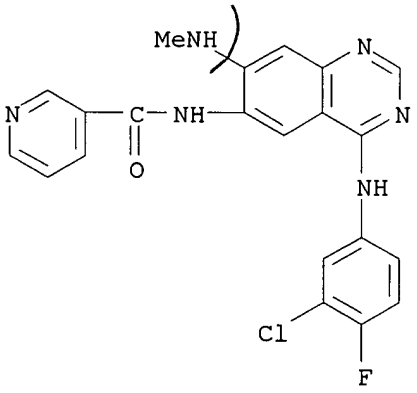
II

AB The invention concerns quinazoline derivs. I [X1 = bond, CO, C(R2)2, CH(OR2), S, C.tplbond.C, O, S, etc.; Q1 = Ph, naphthyl, or 5- or 6-membered heteroaryl optionally bearing 1-3 substituents; m = 1 or 2; R1 = H, halo, CF3, OH, NH2, cyano, etc.; R2 = H, alkyl; Q2 = Ph or 9- or 10-membered bicyclic heterocycle optionally bearing 1-3 substituents] and their pharmaceutically acceptable salts. Also disclosed are processes for prepn. of I and salts, pharmaceutical compns. contg. them, and the use of their receptor tyrosine kinase inhibitory properties in the treatment of proliferative diseases such as cancer. Examples include syntheses of 40 compds. and various intermediates. For instance, Pd(PPh3)4-catalyzed coupling of 6-bromo-4-(3-chloro-4-fluoroanilino)quinazoline-HCl with di-iso-Pr [5-(2-morpholinoethyl)thien-2-yl]boronate (prepns. given) gave 27% title compd. II. At 50 mg/kg/day in athymic nude mice with human vulval epidermoid carcinoma xenografts (cell line A-431), II gave 64% inhibition of tumor vol. (vs. control) after 13 days.

IT **195457-36-4P**, 4-(3-Chloro-4-fluoroanilino)-7-(methylamino)-6-(3-pyridylcarboxamido)quinazoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinazoline derivs. as antitumor agents and antiproliferatives)

RN 195457-36-4 CAPLUS

CN 3-Pyridinecarboxamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-(methylamino)-6-quinazolinyl]- (9CI) (CA INDEX NAME)

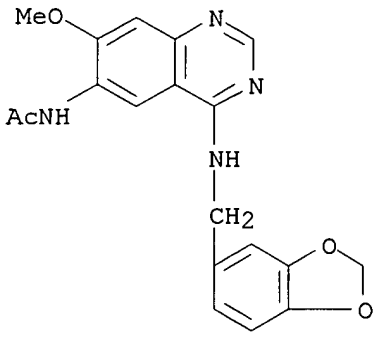


L17 ANSWER 27 OF 27 CAPLUS COPYRIGHT 2003 ACS
AN 1993:603427 CAPLUS
DN 119:203427
TI Preparation of N-containing heterocyclic compounds as phosphodiesterase inhibitors.
IN Takase, Yasutaka; Watanabe, Nobuhisa; Matsui, Makoto; Ikuta, Hironori; Kimura, Teiji; Saeki, Takao; Adachi, Hideyuki; Tokumura, Tadakazu; Mochida, Hisatoshi; et al.
PA Eisai Co., Ltd., Japan
SO PCT Int. Appl., 362 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9307124	A1	19930415	WO 1992-JP1258	19920930
	W: AU, CA, FI, HU, JP, KR, NO, RU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
	ZA 9207465	A	19930413	ZA 1992-7465	19920929
	CN 1071164	A	19930421	CN 1992-110792	19920929
	AU 9226851	A1	19930503	AU 1992-26851	19920930
	AU 668363	B2	19960502		
	EP 607439	A1	19940727	EP 1992-920913	19920930
	EP 607439	B1	20020109		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, SE				
	HU 70854	A2	19951128	HU 1994-910	19920930
	JP 2000264877	A2	20000926	JP 2000-70130	19920930
	JP 2000264885	A2	20000926	JP 2000-70142	19920930
	JP 2000273089	A2	20001003	JP 2000-70138	19920930
	AT 211734	E	20020115	AT 1992-920913	19920930
	US 5576322	A	19961119	US 1994-196110	19940218
	FI 9401417	A	19940325	FI 1994-1417	19940325
	NO 9401101	A	19940530	NO 1994-1101	19940325
	US 5693652	A	19971202	US 1995-408867	19950323
	JP 10095776	A2	19980414	JP 1997-195696	19970722
	JP 3081172	B2	20000828		
	US 5801180	A	19980901	US 1997-904260	19970731
PRAI	JP 1991-320853	A	19910930		
	JP 1993-506780	A3	19920930		
	JP 1997-195696	A3	19920930		
	WO 1992-JP1258	A	19920930		
	US 1994-196110	A3	19940218		
	US 1995-408867	A3	19950323		

OS MARPAT 119:203427
GI For diagram(s), see printed CA Issue.
AB The title compds. [I; R1-R4 = H, halo, (halo)alkyl, (un)substituted cycloalkyl, alkoxy, etc.; R5 = H, OH, hydrazino, alkyl, (un)substituted cycloalkyl, alkoxy, etc.; R6 = H, halo, OH, cyano, alkyl, alkoxy, alkenyl, etc.; A = benzene ring, pyridine ring, cyclohexane ring; B = pyridine ring, pyrimidine ring, imidazole ring], useful for treatment of ischemia, heart attack, hypertension, cardiac insufficiency, and asthma (no data), are prepd. E.g., a mixt. of 4-hydroxy-6-carbamoylquinazoline, SOCl2, and POCl3 was reflexed for 20 h to give 4-chloro-6-cyanoquinazoline. 4-(4-Methoxybenzyl)amino-6,7,8-trimethoxyquinazoline (also prepd.) had an IC50 of 1.0 .mu.M against phosphodiesterase in an in vitro study.
IT **150450-69-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)

(prepn. of, as phosphodiesterase inhibitor)
RN 150450-69-4 CAPLUS
CN Acetamide, N-[4-[(1,3-benzodioxol-5-ylmethyl)amino]-7-methoxy-6-quinazolinyl]- (9CI) (CA INDEX NAME)



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1	CTNF	9
2	892	1
3	1449	3

Total number of pages: 13

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